Day 2

Sunday 1 September 2002

RESYNCHRONISATION THERAPY IN HEART FAILURE: ARE WE DOING ANY GOOD?

77 Sustained clinical efficacy of biventricular pacing in sinus rhythm patients: 2 years follow-up from the MUSTIC study

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Background: Previous controlled and randomized studies have shown that biventricular pacing improved short term (3 to 6 months) functional status in patients with advanced heart failure, intraventricular conduction delay and left ventricular systolic dysfunction. However, few data on long term follow-up are available. The aim of the present study was to evaluate the long term clinical benefit of permanent biventricular pacing (follow up = 2 years) in sinus rhythm patients included in the MUSTIC trial.
Method: The MUSTIC trial was a cross-over (2 x 3 months) designed study to assess the effect of biventricular pacing. After the two cross-over phases, the patient were followed every 3 months in the pacing mode selected according to their preference (biventricular or no pacing). 67 patients in sinus rhythm (63 ± 10 years), all in NYHA class III with a mean LV ejection fraction (LVEF) of 23 ± 7% were included in this study. After completion of the cross-over phases, all patients were programmed in biventricular pacing mode. To date, 35 patients completed the 2-years follow-up
Results:

	Baseline	1 year	2 years
Heart rate (bpm)	75±12	70±10*	70±13*
NYHA class	2.8±0.4	2.1±0.5*	2.1±0.6*
6 min walk (m)	340±97	418±112*	386±150*
Peak VO2 (ml/min/kg)	14±4.5	16.6±3.6*	NA
QOL questionnaire	45±23	30±22*	29±22*
LVEF radionuclides (%)	24±7.7	30±12*	NA

* $p<0.01$ vs baseline, NA = not available

Conclusion: These data show that the short-term functional benefit observed with biventricular pacing in advanced heart failure patients remains stable over 2 years. This therapy seems useful to improve quality of life and exercise tolerance in such patients.

78 Cardiac resynchronization therapy reduces the risk of hospitalization for heart failure and length of stay: results from the MIRACLE trial

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Cardiac resynchronization therapy (CRT) is safe and well tolerated, improves symptoms, NYHA class, quality of life and functional capacity in patients (pts) with HF and ventricular dysynchrony. We examined the effect cardiac resynchronization on the risk of hospitalizations for heart failure and related length of hospital stays. Method. A total of 453 pts were implanted with an InSync cardiac resynchronization system and randomized, 225 pts in the Control group and 228 pts in the CRT group. Pts were required to be on stable medical regimen for at least 1 month prior to enrollment. If on beta-blocker therapy, therapeutic dose maintained was for 3 months prior to enrollment. Initiation or discontinuation of drug therapy during the 6-month control period was discouraged. Results. Results are presented through 6-months follow-up (the double-blind randomization period). There were 34 Control pts with a total of 50 hospitalization days for HF. In the CRT group, there were 18 pts with a total of 25 hospitalization days for HF.

Event	Control (n=225)	CRT (n=228)	p-value
Freedom from use of IV Meds for Worsening HF (95% CI)	83.9% (78.1%, 88.3%)	92.7% (88.4%, 95.5%)	0.004
Freedom from HF Hospitalizations (95% CI)	84.6% (78.9%, 88.8%)	91.5% (86.8%, 94.6%)	0.015
Mean Length of Stay for HF Hospitalizations (days)	7.04 ± 8.41	3.38 ± 3.43	0.024

Conclusion: Pts in the Control group experienced an increase in HF symptoms as evidenced by a greater need for inotropic support and intravenous fluids. This analysis suggests that CRT is associated with a significant reduction in the risk of hospitalization for worsening HF and in the total days hospitalized for HF when compared to the Control group.

79 Cardiac resynchronisation therapy – a cost effective treatment for cardiac failure

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Health care costs for heart failure are substantial.It is the leading medical cause of hospitilisation, accounting for 5% of acute admissions. Heart failure admissions are lengthly,and readmission rates are high, with 20% of patients readmitted within 30 days, and 50% within 3 months. It consumes 2% of the National Health Service budget. Hospital treatment constitutes 65-75% of these costs.Against this background of limited resources, and the need for alternative treatment options, cardiac resynchronisation therapy has emerged.
30-50% of patients with cardiac failure are suitable for resynchronisation therapy. 41 patients have received cardiac resynchronisation therapy in the Belfast City Hospital over a 22 month period, with a mean follow up of 10 months.We recorded the total number of days and the number of heart failure related days spent in hospital, in the 6 months pre and post biventricular pacing, in a group of 22 patients who have reached 6 month follow up period.
Total days in hospital, for all causes, decreased from a total of 511 pre pacing to 111 post($p<0.001$). Admissions for heart failure decreased substantially, from a total of 489 to 19 days($p<0.0003$) in the 6 months following pacing.The mean duration of stay for heart failure before therapy, was 24 days, decreasing to 5.2 days following therapy($p<0.001$). Total number of admissions for heart failure also decreased significantly, from a total of 23 prior to pacing, to 7 following pacing($p<0.002$). Total cost of hospital stay in the 6 month period prior to pacing estimates at £122640. In the 6month period following pacing, this decreased to £26640. Device costs estimate at £66000, thus total costings estimates at £92640.This represents a saving of approximately £30000, a significant cost saving in this group of patients. If the figures are projected onto a larger scale, the savings will be extremely significant.
Conclusions Our initial results are very promising, showing significant reductions in all cause, and heart failure admissions, along with decreased number and duration of admissions. Significant cost savings are also evident. We await the results of larger, longterm follow up trials to fully appreciate the benefits and cost effectiveness of this treatment.

80 Effects of cardiac resynchronization therapy on regional myocardial deformation as measured by echocardiographic strain rate imaging

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Cardiac resynchronization therapy (CRT) aims to improve hemodynamic function in patients (pts) with heart failure (HF) and left bundle-branch block (LBBB) by early stimulaton of late activated regions. Tissue Doppler imgaging (TDI) has been proposed for quantification of asynchrony and patient selection. However, myocardial velocities (V,cm/s) are dependent on overall heart motion. Strain rate (SR,1/s) and strain (S,%) calculation (based on regional velocity gradients) is able to display true regional deformation properties independent of global heart motion and might thus be superior to V for detection of contractile asynchrony. Negative values for SR and S indicate shortening in the longitudinal direction.
Methods: Colour TDI data (>145 frames/s) were obtained from the apical 4-chamber view in 8 HF-pts with LBBB (mean age 64±7, QRS 179±26ms, EF 22±7%) after implantation of a biventricular CRT pacemaker system. Peak systolic V and S, mean SR during ejection (mSR) and the regional delay between QRS onset and peak V (deltaV-t,ms)and peak S (deltaS-t,ms) were compared in mid septal and lateral wall segments during intrinsic conduction (OFF) and during CRT in the same echo examination. Analysis was performed on custom made software, enabling exact timing of global cardiac events.
Results: (table) Peak V and S were severely reduced in both walls. Septal mSR increased and lateral mSR decreased with CRT. Peak regional S was not significantly affected. The delay between septal and lateral peak S was markedly reduced, while the timing of regional peak V was not altered.

	V-sep (cm/s)	V-lat (cm/s)	mSR-sep (1/s)	mSR-lat (1/s)	S-sep (%)	S-lat (%)	deltaV-t (ms)	delta S-t (ms)
OFF	2.4±0.8	1.8±0.5	-0.14±0.3	-0.76±0.3	-13±7	-12±5	60±38	108±68
CRT	2.8±0.4	1.3±0.6¶	-0.5±0.3*	-0.5±0.3*	-9±3	-12±5	62±37	43±34*

*$p<0.05$ vs. OFF, ¶$p<0.05$ versus sep (paired/unpaired t-test)

Conclusions: CRT acutely improved the regional inhomogeniety in mSR and reduced deltaS-t compared to no pacing. We suggest, that these changes in deformation properties reflect the redistribution of regional wall stress and improved contractile synchrony by CRT and may have significant implications for CRT efficacy in this population. In contrast to previous reports, systolic velocities did not display these effects. Strain rate imaging offers new insights in the pathophysiology of LBBB and CRT.

81 Chronic improvement of left ventricular ejection fraction and stroke volume in CHF-patients after CRT by means of 3D-TEE reconstruction

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Background: 3D-transesophageal echocardiography (3D-TEE) offers the possibility to overcome known limitations of conventional 2D echo like geometric assumptions and asynchronous movement patterns. This study evaluated the effects of chronic cardiac resynchronisation therapy (CRT) with respect to left ventricular volume, stroke volume (SV) and ejection fraction (LVEF) in patients (pts) with severely impaired cardiac function and conduction disorders.
Methods: 20 CHF pts were analyzed with 3D-TEE. Etiology of CHF was either idiopathic or ischemic, LVEF<30%, QRS>120ms and NYHA II-IV. During an invasive test, hemodynamic parameters (aortic pulse pressure, LV +dp/dt) were recorded to detect the optimal pacing site and AV-delay for CRT. Pts were implanted with a LV pacing device (either pacemaker or defibrillator) and a LV lead at the optimal determined pacing site. Prior chronic pacing and at 12 month follow up, the pts underwent 3D-TEE to investigate potential differences in LV volume-derived parameters between intrinsic depolarization (ID) and CRT at the optimal AV-delay.
Results: A significant increase ($p < 0.0001$) between baseline-ID and 12month-CRT at the optimal AV delay was found for SV and LVEF at a nearly constant LV enddiastolic volume (LVEDV). SV increased by 45.3% from 43.7±13.7 ml (ID) to 63.5±19.0 ml (CRT). LVEF improved by 47.6% during CRT from 16.4±5.1% (ID) to 24.2±5.9% (CRT). At baseline and at 12monthFu LVEF and SV were significantly improved by CRT compared to ID ($p < 0.0001$).

n=20	Baseline	12 month Fu	% Change	p-value	Unit
LVEF ID	* 16.4 ± 5.1	19.3 ± 5.1	25.9 ± 45.1	0.05	%
LVEF CRT	21.1±5.5	*24.2±5.9	18.4±28.9	0.02	%
SV ID	**43.7±13.7	51.4±16.6	23.2±37.9	0.04	ml
SV CRT	57.2±15.6	**63.5±19.0	14.0±28.7	0.10	ml
LVEDV ID	278.4±89.1	276.7±106.6	0.8±21.0	0.90	ml
LVEDV CRT	283.4±94.7	277.4±108.0	-0.9±21.0	0.66	ml

*,**p<0.0001 Student-t test, mean±sd

Conclusions: 3-D TEE reconstruction of the left ventricle is a feasible method to detect acute and chronic LV volume differences in heart failure pts with wide QRS duration. We demonstrated that acute and chronic CRT significantly improves LVEF and SV. Chronic CRT leads to nearly 50% increase of LV ejection fraction at a nearly constant LVEDV.

CATHETER ABLATION OF VENTRICULAR TACHYCARDIA

104 Mechanisms of ventricular tachyarrhythmia originating from the aortic sinus of Valsalva

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Background: It has recently been demonstrated that the aortic sinus of Valsalva (AS) is one origin for ventricular tachycardia (VT) or extrasystoles (VES). However, the mechanism of this type of tachycardia is still not well defined. The aim of this study was to delineate the different electrophysiological mechanisms of the VT/VES originating from the AS.
Methods and Results: Endocardial mapping was performed in 7 patients (pts; 5 men, mean age: 44 ± 17 years) with symptomatic VT/VES originating from the AS. Adenosine was administered during VT/VES in all pts. Adenosine-sensitive was defined as termination of VT or suppression of VES. Two different reactions to adenosine were found: adenosine-sensitive in 3 pts (group A) and non-adenosine sensitive in 4 pts (group B). In group A, all pts were free of structural heart disease. VT was not inducible by programmed ventricular stimulation in all pts. All successful ablation sites were in the left AS. In group B, there were 2 patients with dilative cardiomyopathy, the other two had no structural heart disease. Five sustained VTs could be induced and terminated by programmed ventricular stimulation. Successful ablation was performed in the noncoronary AS in 3 VTs and in the left AS in 2. Abnormal (diastolic or presystolic) potentials were recorded during sinus rhythm (mean interval from the end of QRS to the potential 121 ± 98 ms) and during VT (mean interval from the potential to QRS 64 ± 45 ms) at effective sites in the AS. Concealed entrainment was demonstrated at all successful ablation sites.
Conclusion: Two different mechanisms may contribute to the development of VT/VES originating from the AS: ATP-trigged activity and reentry. Larger studies are needed to compare the electrophysiological characteristics of both groups.

105 Functional his-Purkinje block: an important mechanism of bundle branch reentrant tachycardia without a prolonged HV interval during sinus rhythm

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Background: The electrophysiological mechanism of bundle branch reentrant tachycardia (BBRT) with a normal HV interval during sinus rhythm (SR) is unknown.
Methods and results: From 178 patients with different types of ventricular tachycardia (VT), 13 were found to have BBRT as the underlying electrophysiological mechanism. Of those 13 patients (9 male, 4 female, mean age 64 ± 13 years), 6 were documented to have a HV interval shorter or equal to 55 ms (group A), whereas 7 had a prolonged HV interval (> 55 ms; group B) during SR. The PR interval (169 ± 32 vs 339 ± 138 ms, p=0.01), the AH interval (101 ± 26 vs 225 ± 126 ms, p=0.04) and QRS duration (116 ± 17 vs 167 ± 29 ms, p=0.003) during SR were significantly shorter in group A than in group B. In group A, the HV interval was significantly longer during VT than during SR (73 ± 18 vs 47 ± 7 ms, p=0.007). There were more patients with functional His-Purkinje block (split His potential, jump of HV interval or phase 3 intra-His-Purkinje block) induced by programmed atrial stimulation or burst pacing in group A than group B (6/6 patients vs 0/7 patients, p<0.001). Successful ablation of the right bundle branch was performed in all 13 patients without deteriorating AV block. During an average follow-up of 27 ± 17 months, 2 patients died in each group and VTs (other than BBRT) or ventricular fibrillation were documented by ICD electrogram storages in 4 patients.
Conclusion: A prolonged HV interval during SR is not a prerequisite for BBRT. Functional conduction block within the His-Purkinje system appears to be the electrophysiological substrate for this type of BBRT. Radiofrequency ablation of the right bundle branch is effective in suppressing BBRT. Despite this, however, ICD-implantation may be still necessary.

106 Cooled tip catheter ablation of epicardial outflow tract tachycardia through the aortic sinus of Valsava

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Monomorphic repetetive tachycardia originating in the LV-outflow tract (LVOT) usually cannot be ablated by a conventional approach due to their epicardial site. The ECG typically shows inferior axis and left bundle branch block pattern. In contrast to RVOT-tachycardia early R/S transition in V3 and a r-wave in V1 can be observed. We describe catheter ablation of epicardial LVOT-tachycardia through the aortic sinus of valsalva (AoSv).
Methods: In 7 pts with highly symptomatic monomorphic VT (5 males, 1 pt with valvular CMP, 5 pts without heart disease) an epicardial site of the arrhythmic focus could be confirmed by pace mapping and earliest local activation within the AoSv. Angiography of the coronary arteries served to define a spacial safety margin with respect to the ablation catheter. High frequency current was delivered using a closed loop irrigated tip catheter system (Chilli Cool®, Boston Scientific). ECG, Holter, Echo and transesophageal Echo (TEE) were performed the following day and after 3 months.
Results: 2 foci were located in the left, 3 in the right and 2 in the acoronary AoSv. Using a target temperature of 40°C a cumulative energy of 203-14953 J was delivered with 2-14 applications. In 6/7 pts acute success could be achieved. Successfully ablated pts were completely asymptomatic during follow-up, no VT could be documented with Holter-ecg. TEE during follow-up could not reveal any damage to the ascending aorta or the aortic valves. In 1 pt only transient suppression of monomorphic VT was obtained. No procedure related complications could be observed.
Conclusions: Monomorphic VT with epicardial origin in the LVOT can be successfully treated by cooled tip catheter ablation through the AoSv. Cooled tip catheter ablation may be favourable in this setting due to its potential to create deep lesions necessary to reach remote foci. Damage to surface tissue may be reduced by lower temperatures at the catheter/tissue interface. Lower temperatures may also reduce the risk of local clot formation which is crucial to all left sided procedures and especially for catheter ablation in the sinus of valsalva.

107 Prediction of future arrhythmic events in patients with cardiac sarcoidosis: role of clinical variables and programmed ventricular stimulation

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Cardiac sarcoidosis is associated with a significant incidence of sudden cardiac death related to ventricular arrhythmias. There is little data on the predictors of sudden death in these patients. The role of clinical parameters and electrophysiology study in predicting future arrhythmic events was determined.
Methods: 25 patients with cardiac sarcoidosis were included in the analysis. Clinical parameters evaluated included age, gender, symptoms (palpitations, presyncope, syncope) presence of non-sustained VT and left ventricular function. All patients underwent programmed ventricular stimulation at 2 ventricular sites with up to triple premature beats. Comparison was performed using the Fisher's exact and Mann Whitney U tests.
Results: Seven patients (28%) were inducible for sustained ventricular arrhythmias. None of the above parameters, including left ventricular ejection fraction, predicted inducibility at electrophysiology study. All inducible patients received implantable defibrillators. Patients were followed for 1 to 128 months (mean 32 months). No patient with an implantable defibrillator died of sudden death during the follow-up. Four of seven patients (57%) with implantable defibrillators received appropriate therapy for ventricular arrhythmias. Mean time from implantation to first event requiring therapy was less than 5 months.
Conclusions: In this patient population with cardiac sarcoidosis, none of the clinical variables studied predict inducibility at electrophysiology study. Patients who are inducible with electrophysiology study are at high risk of potentially fatal ventricular arrhythmias. These arrhythmias can be successfuly treated with implantable cardiac defibrillators, avoiding sudden death.

108 Nonsurgical transthoracic epicardial ablation of incessant ventricular tachycardia: an alternative when other means have failed

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Background: Management of patients with incessant ventricular tachycardia is often a difficult clinical problem. Drugs and radiofrequency catheter ablation are not always effective. A nonsurgical transthoracic epicardial ablation technique recently described can be an alternative in patients refractory to conventional therapy.
Methods AND RESULTS: Since 1998, 14 patients presented with incessant ventricular tachycardia despite the use of 2 or more intravenous antiarrhythmic drugs. In all except one patient who presented an endocardial ventricular thrombus we tried to perform a radiofrequency catheter ablation procedure using the usual endovascular technique. The procedure was effective in 9 patients (69%) and ineffective in 4. In the 4 ineffective patients and in the 1 with the ventricular thrombus, an epicardial ablation approach was used. They were 4 males, 73±7 years old, 4 with ischemic heart disease and 1 with dilated cardiomyopathy. The left ventricular ejection fraction was 30±19% and 4 out of 5 were in refractory heart failure at the moment of the procedure. Three out of the 5 patients previously received an implantable cardioverter defibrillator (ICD). The epicardial ablation was effective in the 4 patients with ischemic heart disease and ineffective in the one with dilated cardiomyopathy who received a cardiac transplantation. No complications occurred. After a mean follow-up of 20±12 months [3-40], a single episode of ventricular tachycardia different to the initial one and successfully treated by the ICD has been documented in one of the patients. No significant differences were found between those with successful endocardial or epicardial ablation.
Conclusions: In patients with incessant ventricular tachycardia despite the use of drugs or standard endocardial ablation, the epicardial approach was very effective and should be considered as an alternative.

109 Epicardial fat tissue does not modify amplitude and duration of the epicardial electrograms and/or ventricular stimulation threshold

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One of the possible reasons for epicardial RF catheter ablation of epicardial circuits to fail is the presence of epicardial fat interposed between the tip of the ablation catheter and the epicardial surface of the heart. Awareness of the presence of epicardial fat could help planning a special strategy to deal with this circuits. The aim of this study was to determine possible modifications caused by the presence of fat tissue in epicardial electrograms and ventricular stimulation threshold. Methods: Bipolar epicardial electrograms were recorded with a standard ablation catheter (distal par of electrodes with a 4 mm tip) during open-chest prior to extracorporal circulation in 10 patients (6 women, 52±6 years/LVEF=43±11%) undergoing CABG surgery. The electrograms were recorded from areas with and without fat tissue as the surgeon firmly hold the catheter against the heart. Then, stimulation threshold was obtained for each one of the areas. Signals were recorded with a filter ranging between 80-500 Hz and a gained of 20mm/mV at a paper speed of 100 mm/sec and analyzed off-line. The layer of epicardial fat was defined as thick if > 5 mm based on a subjective evaluation of the surgeon. Results: Electrograms were obtained from 44 areas without epicardial fat and compared to 45 areas with fat randomically distributed among the free-wall of the left ventricle and the right ventricular outflow tract. The presence of fat does not modify the stimulation threshold among areas with and without fat (4.8±1.6 versus 4.6±1.8 mA. In most areas, peak-to-peak amplitude (40±5 mm versus 43±4 mm) and the duration of the epicardial bipolar electrogram (43.6±5 versus 43.5±6 ms) was not modified by the presence of fat. Stimulation threshold was higher only in areas with a very thick layer of epicardial fat (> 5 mm). Conclusion: The presence of a layer of epicardial fat < 5 mm interposed between the tip of the ablating catheter and the epicardial surface of the heart does not modify the amplitude and duration of the bipolar epicardial electrogram and the epicardial ventricular stimulation threshold.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

114 Apoptosis and structural and metabolic dysfunction or injury of cardiomyocytes in arrhythmogenic right ventricular cardiomyopathy

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The pathogenesis of progressive myocardial atrophy in arrhythmogenic right ventricular cardiomyopathy (ARVC) is not established. Apoptosis, which could be triggered by myocarditis (MC), has recently been suggested as a possible mechanism involved in myocardial loss however, metabolic changes in the myocardium have not been reported.
The aim of the study was to analyse structural and metabolic features and apoptosis of cardiomyocytes in samples from the right ventricle (RV) obtained from patients with recognised ARVC and ARVC with coexisting MC.
Materials and Methods: Samples of the RV free wall obtained by endomyocardial biopsy from 11 paediatric patients (aged from 6 to 17 years) with ARVC recognised according to criteria of McKenna et al. (1994) in whom MC coexisted in 5 cases and samples from 6 patients (aged from 4 to 17 years) with isolated MC who served as controls were investigated. Histopathological evaluation (hematoxylin-eosin and Azan staining) and TUNEL assay were conducted on paraffin sections, histochemical tests (succinic dehydrogenase, SDH, lactate dehydrogenase, LDH, cytochrome oxidase, COX) on frozen sections, and ultrastructural examinations on glutaraldehyde/osmium fixed sections.
Results: Histological examination revealed infiltration of myocardium with fibro-fatty tissue in ARVC but not in MC cases. In some areas of the myocardium histochemistry demonstrated decreased SDH and COX activity correlated with increased LDH activity in both ARVC and MC cases. TUNEL assay showed apoptotic myocardial cells localized in regions invaded by fibro-fatty tissue and also in regions of compact packed cardiomyocytes in ARVC and MC. Ultrastructural study revealed separation of the fascia adherens junctions within the region of intercalated discs in 6, and thinning of the glycocalyx in 5 cases of ARVC, which were not observed in any case of MC.
Conclusions: The occurrence of cardiomyocytes apoptosis in an area not invaded by adipocytes and fibrosis and presence in such areas cardiomyocytes with histochemical features of low metabolic activity and also with membranes separation in the region of intercalated discs and/or thicker than normal glycocalyx may suggest the significance of these features in the pathogenesis of ARVC. However further investigations correlated with clinical signs are necessary to evaluate the role of these findings in the process of myocardial atrophy and/or as prognostic markers in ARVC.

115 Prognostic factors for arrhythmic events in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease)

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Background Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive disease causing life-threatening ventricular arrhythmias. Naxos disease is an autosomal recessive form of ARVC with 100% penetrance. Naxos disease population permits the evaluation of arrhythmic risk during a long term follow-up study.
Methods Twenty-eight consecutive patients (14 men,14 women) with Naxos disease underwent serial cardiac assessment with annual resting 12-lead ECG, 24-h ambulatory ECG and two-dimensional echocardiography in a prospective evaluation of up to 16 years. Historical accurate data were also available from isolated community. Arrhythmic events (syncope and documented episodes of sustained ventricular tachycardia)due to the disease, were studied during a maximum duration of 72 years. T-wave inversion and QRS dispersion (the difference between the widest QRS complex in leads V1, V2 or V3 minus that in V6) were studied on standard 12-lead ECG. Right ventricular dilatation and left ventricular involvement were evaluated from two-dimensional echocardiography. Moreover, ECG and structural progression (progressive alteration in dimensions and/or wall motion abnormalities) were studied. Multivariate analysis was performed using the Cox proportional hazards model. In each patient, gender, age, and ECG/echocardiographic parameters were considered as predictors and the first arrhythmic event was the end point of the study.
Results Arrhythmic events occurred in 17 patients (61%). Median age at first event was 42 years. The results from the survival (event free) analysis are presented in Table 1.

Table 1. Risk factors

Risk factor	Hazard ratio	P-value
QRS dispersion ≥40ms	2,55	0,095
Structural progression	7,38	0,005

Conclusions In autosomal recessive ARVC, the multivariate analysis revealed that QRS dispersion equal or more than 40msec and structural progression were the best predictors for the developement of arrhythmic events.

116 Multielectrode non-contact mapping is an effective tool to define the arrhythmogenic substrate in patients with right ventricular tachycardia

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Background: Characterization of the substrate functionally involved in right ventricular tachycardia (VT) is limited by point-by-point conventional contact mapping. For this reason, we evaluated the efficacy of a multielectrode non-contact mapping method, capable of simultaneous endocardial mapping of the entire right ventricle, to identify the critical components of the arrhythmia.
Methods: The electrophysiological (EP) characteristics pointed by the non-contact mapping system "Ensite 3000" (Endocardial Soutions) in 28pts (14M, age 40±15yrs) undergoing radiofrequency catheter ablation (RFCA) for VT are reported. According to guidelines diagnostic criteria, 10pts were classified as having arrhtyhmogenic right ventricular dysplasia (ARVD, Group A), 18pts as idiopathic (Group B). Beside conventional EP study, with respect to right ventricular endocardial activation-mapping, the following parameters were analyzed: in sinus rhythm, -delayed activity on virtual unipolar electrograms; during VT, -evidence of a diastolic pathway (activation of a "channel" of endocardium over the diastolic interval) at virtual unipolar electrograms/isopotential color maps, and, -discrete presystolic activity from exit point with radial spread in the surrounding myocardium, in the same unipolar mode. 42 VTs (21, 2.1±0.9/pt, in Group A; 21, 1.2±0.5, in Group B; cycle 269±77ms) were induced (12VTs non-tolerated, 11 non-sustained).
Results: Delayed sinus rhythm activity was detected in 10/10pts (100%; 45±37ms, Group A), and in 4/18pts (22%; 30±20ms, Group B) ($p<.001$). The diastolic pathway was identified in 16/21VTs (76%) vs. 3/21VTs (14%), in Group A and B respectively ($p<.005$). Presystolic activity with "QS" morphology -preceding QRS onset by 38±14ms-, followed by rapid breakout, was found in 0/21VTs (Group A) and 18/21VTs (86%, Group B) ($p<.001$). Interestingly, all 3pts in Group B with VT marked by diastolic pathway, showed no presystolic "focal" activity, 2/3 had delayed activation in sinus rhythm, and 3/3 had an uncommon presentation for idiopathic VT (2 morphologies, 1 with intermediate/superior axis induced by programmed stimulation). RFCA was acutely successful in 5/10 (50%) and in 19/21 (90%) pts (Group A and B, respectively; $p<.05$). No complication occurred.
Conclusions: Multielectrode non-contact mapping is effective to characterize the arrhythmogenic substrate in pts with VT and may document reentry even in absence of ARVD. This may suggest that non-contact mapping helps identifying early forms of disease and improve RFCA efficacy especially in this group of pts.

117 Radiofrequency catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy: long-term outcome

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Introduction: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a degenerative disease affecting the right ventricle and less often the left ventricle. Thinning of the RV wall and fatty replacement of myocardial tissue can be detected by MR imaging. Ventricular tachycardia (VT) often occur in pts with ARVC and can be treated with radiofrequency catheter ablation (RFCA). This study evaluates both short- and long-term results of RFCA of VT in ARVC patients. Methods: From 1997 until 2001, 41 consecutive pts (26 male, age 47 ±14 yrs) underwent RFCA of drug refractory VT in ARVC. In all pts the diagnosis of ARVC was established by MR imaging. Results: In total 94 different VT's were induced and targeted for ablation during the procedures (2.3±1.9 morphologies per pt). Procedural success (defined as non-inducibility of VT after the procedure) was achieved in 88% of the pts. The procedure and fluoroscopy times were 176±73 and 34±21 minutes respectively. Serious procedure-related complications were observed in 3 (7%) pts: myocardial perforation during RF application occurred in 3 pts, 2 pts underwent immediate surgery; 1 pt recovered after pericardiocentesis. One pt (after surgery) died <48 hrs after the procedure due to cardiogenic shock. Before discharge, 3 pts (7%) underwent ICD implantation either for hemodynamically non-tolerable VT/VF and/or a non-successful ablation procedure. During follow-up (18.5±19.4 months), a recurrence of VT was observed in 7 pts (18%, 86% new VT morphology). No pt died during follow-up. Conclusion: RFCA of VT in pts with ARVC is a successful and relatively safe procedure. The recurrence rate is still high, which might be explained by the progressive nature of the disease. As none of the patients died suddenly a selective ICD implantation approach in these patients is justified.

118 Catheter ablation in arrhythmogenic right ventricular cardiomyopathy: what to gain and what remains?

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In pts with arrhythmogenic right ventricular cardiomyopathy (ARVC), the role of catheter ablation for treatment of ventricular tachycardia (VT) is still controversial. Therefore, we analyzed the acute success and the long-term results during follow-up of up to 15 years after catheter ablation in 43 pts with ARVC. Indications for catheter ablation were incessant VT or very frequent VT recurrences (mainly associated with frequent shocks from an implanted ICD) in 8 pts (19%), drug-refractory VT in 32 pts (74%), and as primary treatment in 3 pts (7%). 21 pts had extensive forms of ARVC with severe global and/or regional RV dysfunction.
Catheter ablation of the targeted VT was acutely successful in 34 of 43 pts (79%). Incessant or very frequent VT was clinically controlled in all of the 8 pts with either no (n=2) or only sporadic subsequent VT recurrences. During follow-up of up to 15 years (mean: 102±20 months), 2 pts died and 32 pts (74%) experienced recurrent VT or VF. Survival rates free of arrhythmic events were 63%, 42% and 31% after 1, 3, and 5 years, respectively. Pts with localized ARVC showed better long-term results than those with extensive RV dysfunction ($p<0.01$). In pts initially considered effectively treated by catheter ablation, the majority of relapses were due to "new VT" that showed different morphologies when compared to the targeted VT during the ablation sessions. These "new VT" may therefore represent new arrhythmic foci that developed during the progressive long-term course of ARVC.
Conclusions: In pts with ARVC, catheter ablation yields high acute success rates for the effective treatment of the targeted VT. Optimal indications for catheter ablation in ARVC are incessant VT or frequent recurrences of VT (ie, causing frequent ICD shocks). These complex clinical situations can be effectively controlled acute and long-term by catheter ablation as the treatment of choice. However, long-term freedom of VT recurrence after catheter ablation in ARVC is rare due "new" VT morphologies during follow-up, reflecting the progressive nature of ARVC particularly in pts with severe RV dysfunction.

119 Problems associated with and long-term effectiveness of implantible cardiac defibrillator therapy in patients with right ventricular dysplasia

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Right ventricular dysplasia (RVD) leads to a significant incidence of recurrent ventricular tachycardia (VT) and sudden cardiac death. Problems associated with and long-term effectiveness of implantible cardiac defibrillators (ICDs) in RVD patients were evaluated.

Twenty-four patients undergoing ICD implantation were included in this analysis. Group one included 12 patients with RVD and group two included 12 ischemic cardiomyopathy controls. Mean follow up was 4.6 years in patients with RVD and 4.2 years in patients with ischemic cardiomyopathy. Parameters compared included: final R wave sensitivity, impedance, pacing threshold, defibrillation threshold, post-implantation deaths, recurrent ventricular arrhythmias requiring therapy and antiarrhythmic drugs used.

Patients with RVD were younger (mean age 53±17 vs. 66±11, $p<0.03$) and had greater left ventricular ejection fraction (54±10% vs. 25±10%, $p<0.001$). Gender distribution and indication for ICD implantation were similar across the two groups. At implantation, RVD patients had lower final R wave amplitudes (6.9±2.4mV vs. 14.3±6.0mV, $p<0.001$). There was no significant difference in lead impedance, pacing thresholds (0.74±0.29V vs. 0.6±0.17V) or defibrillation thresholds (14.4±5.5J vs. 14.0±2.9J). At follow-up, RVD patients experienced a greater number of ventricular arrhythmias (34±61 episodes vs. 16±30 episodes) and required a greater number of antiarrhythmic medications for VT suppression (2.6 drugs vs. 1.4 drugs per patient, $p<0.05$). There were no documented episodes of inadequate sensing in RVD patients and no patient died of ventricular arrhythmia in either group. One patient with ischemic cardiomyopathy died of congestive heart failure and one patient with RVD died of pulmonary embolism. A second patient with RVD also experienced a nonfatal pulmonary embolism.

Conclusions: Patients with RVD have lower final R wave sensing thresholds. However, the lower R wave sensing leads to no significant adverse outcome. Although ICD therapy is effective in terminating ventricular arrhythmias in patients with RVD, the frequency of recurrent episodes often mandates an increased use of antiarrhythmic medications. In addition, patients with RVD may be at high-risk of pulmonary embolism after lead implantation. Long-term anticoagulation should be considered in patients with large right ventricles.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS IN PRIMARY AND SECONDARY PREVENTION

120 Implications of national guidance on the implantation of implantable cardioverter-defibrillators for arrhythmias

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Background: Based on published trial data, the National Institute for Clinical Excellence (NICE) published guidance on the use of implantable cardioverter defibrillators (ICDs) in the UK in September 2000. This estimated that a total implantation rate of 50 devices/million/year (equivalent to 33 to 39/million/year first implants) would be required to implement its recommendations.

Methods: We have audited all cardiac patient contacts with our ICD implanting centre over a month and subsequently all admissions to the 3 coronary care units serving our district over a second month against the published standards of the NICE guidance.

Results: Full implementation of the guidance would have required significant increases in post-MI screening (a 4% increase in echocardiography, a 59% increase in Holter monitoring and a 376% increase in VT stimulation studies) and resulted in a more than 420% increase in ICD implantation.

The incidence of new ICD indications in our district was 105/million/year. This is approximately 3-times the implant rate for first devices anticipated by NICE and 7-times the current UK implant rate. If the NICE guidance were amended to include MADIT II criteria, this would at least double these figures.

Implications of NICE guidance

	Echo	Holter	EPS	ICD
Performed	737	126	5	5
Additional	30	75	19	21
TOTAL	767	201	24	26

Echo = 2D echocardiography, Holter = 24-hour ambulatory ECG monitoring, EPS = Ventricular tachycardia stimulation electrophysiology study, ICD = implantable cardioverter defibrillator implantation

Conclusion: Full implementation of the conservative guidance issued by NICE would require very significant increases in post-MI screening and result in a dramatic increase in ICD implantation in the UK to approximately the level seen in the USA. The personnel, equipment and financial resources required to achieve this exceed those available in our centre and those anticipated by NICE. As recommended in the guidance, this audit process should be repeated in other centres to facilitate planning of evidence-based ICD therapy in the UK.

121 What reduction in mortality can we expect from the ongoing primary prevention implantable cardioverter-defibrillator trials?

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Results from MADIT demonstrated that mortality can be significantly reduced in highly selected pts. with remote MI by an ICD. Ongoing and just terminated primary prevention trials use various non-invasive inclusion criteria and enrol pts. early after acute MI prior to hospital discharge. It is however unclear, to what amount total mortality can be reduced by an ICD that prevents solely from sudden cardiac death (SCD).

Purpose: We sought to determine the effect of SCD prevention on total mortality in high risk post MI pts. as defined in the different primary prevention trials.

Method: We stratified a consecutive series of 790 post MI pts. <75 years (males 76%, mean age 59±10 yrs.) from our MI data base according to various non-invasive selection criteria. Clinical data: anterior MI 45%, transmural MI 80%, thrombolytic therapy 59%, PTCA 39%, ACVB 11%. A Kaplan-Meier survival analysis was performed for a median duration of 27 months including careful analysis of the mode of death according to the EMIAT classification. Holter ECG and determination of EF was performed prior to hospital discharge (10±6 days after MI). Risk groups were defined according to the following criteria: Ejection fraction (EF) ≤35% + nonsustained ventricular tachycardia (nsVT) on Holter ECG, EF≤30%, EF≤35% + Holter mean HR ≥80/min, and nsVT≥150/min on Holter.

Results: Two-year total mortality was 43.0% (EF<35+nsVT), 24.0% (EF<30), 24.7% (EF<35+HR>80), and 27.6% (nsVT>150). The corresponding rates of the 2-years SCD rate are 10.2% (EF<35+nsVT), 6.5% (EF<30), 7.6% (EF<35+HR>80), and 12.7% (nsVT>150). Mortality and SCD rate were significantly higher in comparison to all respective control groups ($p<0.0001$). The portion of SCD at total mortality in the high risk groups was 23% (EF<35+nsVT), 27% (EF<30), 31% (EF<35+HR>80), and 46% (nsVT>150).

Conclusion: A significant reduction of total mortality from 23% up to 46% can be expected from prophylactic ICDs according to the inclusion criteria used. This estimated reduction rate is in good agreement with recently reported data.

122 High risk of ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy, reduced ventricular function and non-sustained ventricular tachycardia

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The value of prophylactic ICD-therapy for patients with an idiopathic dilated cardiomyopathy without survived sudden cardiac death and without documented sustained VT is yet not clear. Besides, the prognosis of patients with an idiopathic dilated cardiomyopathy, severly depressed left ventricular function and non-sustained VT has not been sufficiently studied. Aim of the present study was to assess the incidence of ventricular tachyarrhythmias in those patients after implantation of an ICD irrespective of inducibility at programmed stimulation.

Patients and methods: A total of 25 patients with an idiopathic dilated cardiomyopathy were followed over a mean follow-up of 22±19 months. The mean ejection fraction was 22±12%. In none of the patients sustained VT or syncope had been documented. All patients had only presented with non-sustained VT during Holter-ECG. In 23 patients programmed ventricular stimulation was performed. In 26% a monomorphic VT was inducible. Ventricular fibrillation was induced in 17% of the patients. All patients received an implantable defibrillator. Results: In 9/ 25 patients (36%) 26 episodes of ventricular tachycardia or ventricular fibrillation occurred duing follow-up with a mean of 2.9 episodes per patient. 30% of the patients who had been inducible in programmed ventricular stimulation had a VT event vs. 46.2% of the patients who were not-inducible. In all patients the ventricular tachyarrhythmia was successfully terminated by the implantable defibrillator terminated.

Conclusion: 1. The incidence of ventricular tachycardia or ventricular fibrillation in patients with dilated cardiomyopathy, severely depressed LV function and documented NSVT is 36%. 2. Inducibility does not predict a worse outcome and non-inducible patients had a higher likelihood of VT/VF. 3. There should be prospective trials in this subgroup of patients, who had no syncope, no documented sustained VT, but NS-VT only, since these patients seem to be at a high risk of sudden death.

123 Elevated heart rate preceding the onset of ventricular tachycardia influences ATP effectiveness in patients with implantable cardioverter-defibrillators

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Background: The incorporation of antitachycardia pacing (ATP) into implantable cardioverter defibrillators (ICD) has provided a better tolerated alternative to shocks. ATP has been shown to be effective in terminating approximately 80-90% of spontaneous ventricular tachycardia (VT) episodes. Although ATP is routinely used, little is known about predictors of ATP failure. We aimed to prospectively follow-up patients with ICDs, and to analyze parameters affecting ATP effectiveness.
Methods and Results: Consecutive 118 patients received ICDs for standard indications. Prior to discharge, empirical, standardized ATP therapy was programmed in all patients within VT zones. A total of 1218 spontaneous tachycardia episodes occurred in 51 patients during a mean follow-up of 24.5 ± 12 months. Among these, 888 monomorphic VT episodes were diagnosed. One hundred and four fast VTs were detected in the VF zone and treated with primary shock delivery. ATP was attempted 881 times in the remaining 784 VT episodes. ATP terminated 640 VTs successfully, ATP failed in 55 VTs finally reverted by shocks, and 89 VTs converted to a slower VT outside the VT zone. Fifty-one of these slower VTs reverted spontaneously, and 38 were redetected and treated. Finally, in primary intention-to-treat, ATP was successful in 691 VTs (subgroup ATP+), and unsuccessful in 93 VTs (subgroup ATP-). There were no influence of VT cycle lengh on ATP success rate. Furthermore, ATP efficacy was similar between patients with left ventricular EF less or equal to 35% or > 35%, as well as between patients with ischemic or nonischemic cardiomyopathy. Heart rate immediately preceding the onset of VT was found being the sole parameter affecting ATP effectiveness. Indeed, heart rate was faster in the subgroup ATP- compared to the subgroup ATP+ (103 ± 19 bpm vs 78 ± 14 bpm, respectively, $p < 0.0001$). Interestingly, ATP therapy was less successful among patients discharged without betablockers compared to betablocker-treated patients (79% vs 95%, respectively, $p < 0.0001$).
Conclusions: The present study demonstrates that elevated heart rate preceding the onset of VT, suggestive of an increased sympathetic tone, is the sole parameter affecting ATP effectiveness in patients with ICD.

124 Prognostic significance of electrical storm in patients with implantable cardioverter-defibrillators

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Background: Electrical storm (ES), multiple appropriate therapies (antitachycardia pacing and/or shocks) during a short time period, has been shown to be a frequent problem among recipients of implantable cardioverter defibrillators (ICDs). Some controversy exists today regarding its prognostic significance. This study was undertaken to provide data on incidence and prognostic significance of ES in ICD patients.
Methods and Results: Baseline characteristics of 307 patients with standard indications of ICD were prospectively collected, and chart reviews and episode data retrospectively analyzed. ES was defined as > or equal to 2 ventricular tachyarrhythmias within 24 hours. During a mean follow-up of 39 ± 32 months (median 27, range 7 to 152 months), 123 patients (40%) experienced 294 episodes of ES (2.4 ES/patient). This arrhythmia clustering occurred at an average of 27 ± 25 months after ICD implantation (median 17 months, range 0.07 to 120 months), and most episodes (90%) were due to ventricular tachycardia. Fifty-two patients (42%) suffered one ES episode, and 71 (58%) had > or equal 2 ES episodes. Characteristics and survival of ES patients were compared to those of ES-free patients. Fifty-tree patients died during the follow-up period. The cumulative probability of survival as estimated by the Kaplan-Meier method for the 307 studied patients was 92.3%, 84%, 82.3% at 1, 5 and 10-year follow-up, respectively. The number of all cause and cardiac deaths were 26 and 20, respectively, in the ES group, and 27 and 20, respectively, in the ES-free group. There were no significant difference in actuarial survival at 1, 5 and 10-year follow-up between the two groups. Seventy-nine percent of storm patients were alive at 10-year follow-up compared to 85% of ES-free patients.
Conclusions: ES is a frequent and recurrent trouble in ICD patients, can occur at any time during the follow-up period, and does not seem to be associated with an increased mortality.

125 The comparative efficacy of implantable cardioverter-defibrillator for primary and secondary prevention of sudden cardiac death

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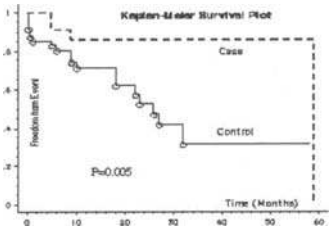
Primary prevention of sudden cardiac death (SCD) is an accepted indication for ICD implantation.

Objective: The purpose of this case-control analysis is to evaluate the frequency of appropriate use of prophylactic ICD and the appropriateness of current risk stratification schemes. We estimated the frequency of appropriate ICD therapy in primary versus secondary ICD use; 39 patients received an ICD for prophylactic reasons including coronary artery disease with non-sustained VT (23%) or with low heart rate variability (21%) or clinical heart failure and low left ventricular ejection fraction (23%) or unexplained syncope with low left ventricular ejection fraction and dilated cardiomyopathy (33%). Cases were matched to 53 controls, which received an ICD for secondary prevention of episodes of documented sustained tachyarrhythmias, according to age (mean 62±15 vs 62±10 years), left ventricular function (mean 34±14 vs 34±13%), underlying coronary artery disease (72 vs 73%) and beta-blocker use (87 vs 87%) respectively.
Results: Over a mean follow up period of 18 months and 37 months for cases and controls respectively, appropriate therapy (antitachycardia pacing and/or shock) occurred in 13% of cases and 42% of controls(p=0.0029),(Kaplan-Meier curve). The median time to first appropriate therapy was 8 months and 12 months for cases and control respectively(p=0.5). Actuarial one-year mortality was 2.6%(N=1), 7.5% (N=4) for cases and control respectively (p=0.3).



Kaplan-Meier survival plot.

Conclusion: Patients receiving ICD for primary prophylaxis receive appropriate therapy significantly less often than matched patients receiving ICD for secondary prophylaxis.

MECHANISMS FOR MODULATION OF VASCULAR FUNCTION IN TYPE II DIABETES

169 Effects of low-dose ramipril on cardiovascular events in type 2 diabetes patients with microalbuminuria/proteinuria: the DIABHYCAR study

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High Urinary Albumin Excretion (UAE; microalbuminuria/proteinuria) predicts cardiovascular and renal events in type 2 diabetes patients. The ACE inhibitor ramipril at low dose reduces high UAE in these patients. To examine whether ramipril 1.25 mg/day may reduce the predicted risk, we conducted the DIABHYCAR (DIABetes, HYpertension, CArdiovascular events and Ramipril) study, a multicenter, multinational, placebo-controlled, parallel trial with ramipril 1.25 mg/d on top of the usual treatment in 4912 normotensive or hypertensive type 2 diabetes patients (men or women, aged > 50 years), selected because of permanent high UAE (> 20 mg/L) and plasma creatinine < 150 μM. The primary endpoint was the composite of cardiovascular death, myocardial infarction, stroke, acute heart failure requiring hospitalization, or end-stage renal failure. The study lasted >3 years (median 4.5 y), and study power to detect a 20% difference between the groups was calculated to be at least 85%. Seven hundred thirty nine primary endpoint events were observed (3.83/100 patients-years). No significant effect of Ramipril 1.25 mg was detected on either the primary endpoints [risk ratio (RR) = 0.97 (95% CI 0.85-1.11], or cardiovascular death [RR 1.07 (95% CI 0.85-1.35)], myocardial infarction [RR 0.89 (95% CI 0.61-1.29)], stroke [RR 1.07 (95% CI 0.80-1.44)], acute heart failure [RR 0.84 (95% CI 0.62-1.14)], or end-stage renal failure [RR 0.40 (95% CI 0.13-1.30)]. At one year, blood pressure had decreased by 2.1/1.0 mmHg in the ramipril compared with placebo ($p < 0.001$/ns). The proportion of patients who had proteinuria (UAE > 200 mg/L) at the end of study was 29.1% in the ramipril vs 32.6% in the placebo group ($p = 0.057$). The DIABHYCAR study complements the MICRO-HOPE results by showing that cardiovascular and renal risks need a full dose of ACE inhibitor to be reduced in type 2 diabetes.

170 PPARγ-ligands inhibit endothelial cell migration mediated by different chemoattractants via inhibition of Akt and eNOS

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Peroxisome proliferator-activated receptor gamma (PPARγ) plays an important role in the regulation of glucose metabolism and exerts several vascular effects that may provide a dual benefit of this receptor on metabolic disorders and vascular disease. Activating ligands of PPARg include the antidiabetic thiazolidinediones troglitazone and ciglitazone, which have been shown to inhibit vascular smooth muscle cell migration. Migration of endothelial cells in response to various angiogenic factors plays a critical role in the pathogenesis of late atherosclerotic lesions, since it contributes to neovascularization of the atherosclerotic plaque. It was therefore the aim of this study to investigate the effects of PPARg-ligands on endothelial cell migration induced by different migration factors and to examine the chemotactic signaling pathways involved. Using VEGF (20 ng/ml) or leptin (50 ng/ml) as chemoattractants, we observed a significant increase in directed migration of human umbilical vein endothelial cells (EC) by 4.3-fold, or 2.1-fold, respectively (all $p<0.05$). EC migration in response to both migration factors was dose-dependently inhibited by the PPARγ-ligands troglitazone (TRO, 1-20 μM) and ciglitazone (CIG, 1-20 μM), and almost completely blocked at their highest concentrations (all > 95%, all $p<0.05$). To elucidate which chemotactic signaling pathway was affected by the PPARγ-ligands, we next looked at their effects on signal transduction through the phosphatidyl inositol 3 kinase (PI3K) -> Akt -> endothelial nitric oxide synthase (eNOS) pathway and the p42/44 mitogen activated protein kinase (MAPK) → myosin light chain kinase (MLCK) pathway, both of which being known to be required for endothelial cell migration. Inhibition VEGF- or leptin-directed EC migration by the pharmacological PI3K-inhibitor wortmannin (100 nM) or the p42/44 MAPK inhibitor PD98059(30 μM) was confirmed in migration experiments (all > 90%, all $p < 0.05$).

Both, TRO (20 μM) and CIG (20 μM) significantly inhibited VEGF- and leptin-induced phosphorylation of the protein kinase Akt and its downstream target eNOS, whereas phosphorylation and activation of p42/44 MAPK and MLCK in response to the migration factors was not affected by any of the PPARg-ligands. Our study identifies, that PPARγ-ligands inhibit chemotactic signal transduction in EC by targeting the PI3K →Akt→ eNOS pathway. By inhibiting EC migration PPARγ-ligands may protect the vasculature from pathological alterations associated with metabolic disorders.

171 Growth factor- and cytokine-mediated regulation of PPARγ in human monocytes

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The nuclear hormone receptor peroxisome proliferator-activator γ (PPARγ) is expressed as two isoforms (PPARγ 1 and 2), is upregulated in atherosclerotic lesions, and an important regulator of monocyte function. Since little is known about growth factor-mediated regulation of PPARγ in monocytes, we studied the regulation of PPAR γ 1 and 2 by different growth factors and cytokines in human peripheral blood monocytes (HPBM) and human THP-1 monocytes.

Human THP-1 monocytes were treated with Angiotensin II (AngII, 1μmol/L), Transforming growth factor-beta1 (TGF-β1, 5ng/ml)), Tumor necrosis factor alpha (TNFα, 10ng/ml), Monocyte chemoattractant protein 1 (MCP-1, 50ng/ml), and C-reactive Protein (CRP, 200μg/ml)). In western immunoblotting experiments, treatment with AngII, TNFα, MCP-1, and CRP showed no effect on PPARγ 1/2 protein expression. Whereas TGF-β1 induced PPARγ 1/2 protein expression by 3.8±0.2-fold in THP-1 cells and by 2±0.1-fold in HPBM after 24h (both $p<0.05$). RNAse protection assays in THP-1 monocytes demonstrated that TGF-β1 (5ng/ml) predominantly induced PPARγ2 mRNA after 2h stimulation with a maximal induction of 14.8±2-fold after 24h ($p<0.01$), whereas PPARγ1 mRNA was only induced by 2.2±0.2-fold after 24h ($p<0.05$). Transient transfection experiments revealed that TGF-β1 (5ng/ml) activates transcription from a PPARγ2 promoter/ luciferase reporter vector by 3.4±0.1-fold ($p<0.05$). Mutation of two CCAAT/ enhancer binding protein (C/EBP) consensus recognition sites reduced the inductive effects of TGF-β1 by 67.4±6.2% ($p<0.05$). To examine if TGF-β1-upregulated PPARγ is transcriptionally active, we performed transient transfection experiments with a PPAR response element (PPRE) driven acyl-CoA oxidase-Tk-luciferase reporter plasmid. TGF-β1 (5ng/ml) alone stimulated PPRE activity by 2.1±0.1-fold, which was further stimulated by the synthetic PPARγ-ligand Rosiglitazone (10μM) to 4±0.3-fold (both $p<0.05$).

The present study demonstrates that TGF-β1 induces monocytic PPARγ1/2 with a predominant stimulation of PPARγ2, which is mediated through a transcriptional mechanism involving C/EBP. TGF-beta1-mediated induction of PPARγ 1/2 in monocytes may play an important role for PPARγ regulation and function in atherosclerotic lesions.

172 Hyperglycemia-induced oxidative stress and vascular inflammation via protein kinase C activation

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The link between diabetes mellitus and premature cardiovascular disease is well established. Loss of the modulatory role of the endothelium may be an initiating factor in the development of diabetic vascular complications. Hyperglycemia, which is recognized as the culprit in the pathogenesis of diabetic vascular disease triggers the endothelial dysfunction. The molecular mechanisms by which high glucose reduces availability of NO, increases reactive oxygen species (ROS) generation and stimulates proinflammatory endothelial changes remain poorly understood. This study was designed to investigate the underlying intracellular signaling pathways. Human aortic endothelial cells were exposed to control (5.5 mM) or high glucose (22.5mM) for 48 hours. Protein kinase C (PKC) assay system was performed in cell homogenates. The intracellular formation of ROS was detected using the fluorescent probe H2-DCFDA. Nuclear factor-kB (NF-kB) activity was assessed by gel shift assay. Expression of P-selectin, ICAM-1, VCAM-1 and monocyte chemoattractant protein-1 was measured by Western blotting. Glucose-induced increase of membrane-bound PKC activity (191% vs control, n=4, $P<0.05$) was associated with subsequent generation of ROS (10436±2101 vs 24893±3996 relative units for control and high glucose respectively, n=6, $P<0.05$). Accordingly, N-acetylcysteine (50 mmol/L) and vitamin C (100 mmol/L) did not affect glucose-induced activation of PKC, whereas inhibition of PKC with calphostin C (3x10-7 mol/L) abolished glucose-induced generation of ROS (9820±1121 relative units, n=6). The glucose-induced and PKC-dependent oxidant generation caused NF-kB activation (297±71% vs control, n=3, $P<0.05$). Indeed, the increase of NF-kB activity was abolished by calphostin C as well as N-acetylcysteine (84±22 and 123±33%, respectively). Furthermore, high glucose significantly increased the level of P-selectin (200±69% vs control,$P<0.05$, n=3), ICAM-1 (156±5% vs control, $P<0.01$, n=3) and VCAM-1 (164±26% vs control, $P<0.05$, n=4). Phorbol 12-myristate 13-acetate (PMA, 10-6 mol/L) induced an increase of adhesion molecule expression similar to that elicited by glucose. The effect of glucose and PMA was totally reversed by co-incubating the cells with calphostin C. Protein level of monocyte chemoattractant protein-1 in cells exposed to high glucose was also increased (149±8% vs control, $P<0.001$, n=4). Our results show that intracellular PKC-signaling pathway is the proximal step for hyperglycemia-induced endothelial redox and inflammatory changes.

173 A novel proinflammatory pathway involving the signal transduction sequence of S100A8/S100A9-RAGE-MAPK-NFkappaB

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Atherosclerosis is an inflammatory disease in which a perpetuated activation of NFkappaB via the RAGE (receptor for advanced glycation end-products)-MAPK signaling pathway may play a central pathogenetic role. As recently Ca^{2+} binding proteins of the S100 family have been identified as novel ligands of RAGE we sought to determine the effects of the proinflammatory heterodimer of S100A8/S100A9 on the RAGE-NFkappaB mediated activation of proinflammatory molecules. Endothelial cells (HUVEC) were preincubated for 72 h with AGE-albumin or albumin for control, whereas AGE-albumin induction resulted in a dramatic upregulation of RAGE. Following this preactivation, cells were stimulated for 48 h with human recombinant S100A8/S100A9. Control stimulations were performed with S100A8 and S100A9 homodimers respectively as well as with S100A1 and S100B. Culture supernatants were screened for IL-6, ICAM-1, VCAM-1 and MCP1 secretion. Heterodimeric S100A8/S100A9 dose dependently enhanced secretion of IL-6, ICAM-1, VCAM-1 and MCP1 in AGE-albumin pretreated HUVEC. These effects could not be detected after stimulation with the homodimeric proteins S100A8, S100A9, S100A1 and S100B. While secretion of IL-6, ICAM-1, VCAM-1 and MCP1 was significantly reduced by PD98059 (30 μM) or simvastatin (10 μM) indicating both a ras and ERK1/2 associated effect of heterodimeric S100A8/S100A9, no effect was seen with SB203580 (20 μM), an inhibitor of the p38/SAPK-pathway. The stimulation of AGE-albumin pretreated HUVEC with the heterodimeric S100A8/S100A9 thus results in a proinflammatory endothelial response which is apparently conveyed by a ras/ERK1/2 dependent signal transduction pathway. These observations appear to be specific since the application of other members of the highly conserved S100 protein family did not exert a proinflammatory response. The heterodimeric proinflammatory protein S100A8/S100A9 might thus play a hitherto unknown but central role in the propagation of NFkappaB associated proinflammatory events triggering atherosclerosis in diabetes and renal failure which are pathophysiological entities associated with a high AGE burden. Thus blocking the proinflammatory activity of S100A8/S100A9 might represent a novel therapeutic modality in treating atherosclerosis.

174 Increased vascular oxidative stress in patients with type II diabetes mellitus is mediated by protein kinase C

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Increased oxidative stress may contribute to vascular pathology in patients with type II diabetes mellitus. We have previously shown that oxidative stress in diabetes is mediated by primarily vascular NADPH oxidase, but the mechanisms leading to an increased NADPH oxidase activity remain unclear. We aimed to study the role of vascular protein kinase C (PKC) in mediating NADPH activity in arteries of patients with diabetes.

Methods: Segments of internal mammary artery (IMA) were obtained from 25 patients with non-insulin dependent diabetes (DM) and 25 non-diabetic patients (nonDM) (matched for other risk factors, cholesterol levels, age, sex, and MI) undergoing bypass graft surgery. Both basal and NADPH-stimulated (100μM) superoxide generation was measured using lucigenin enhanced chemiluminescence (5μM) and by dihydroethidium staining in frozen cryosections. Results: Both basal and NADPH-stimulated superoxide generation were significantly higher in IMA from DM patients. Dihydroethidium staining showed that increased superoxide production in DM vessels was observed predominantly in the endothelium and to the lesser extent in the media. Superoxide production was abolished by preincubation with NADPH oxidase inhibitors DPI (10μM) and apocynin (1mM). Moreover, incubation of vascular segments with chelerythrine (3μM), an inhibitor of PKC, significantly inhibited both basal and NADPH stimulated superoxide generation (table). This inhibition was much more marked in diabetic than in non diabetic vessels (63±6% vs 28±5%; $p<0.01$ for basal). PKC inhibitor abolished the difference in both basal and NADPH stimulated superoxide generation, between DM and non DM vessels.

	nonDM-basal	non DM-NADPH	DM basal	DM - NADPH
native	20.4±2.9	1499±244	29.9±4.5*	2844±718*
+ chelery(3uM)	14.6±2.1	919±365	11.1±1.9	1489±533
p value	0.04	0.02	0.001	0.002

*-$p<0.05$ vs non DM

Conclusions: Our results suggest that protein kinase C signaling plays an important role in mediating increased activity of vascular NAD(P)H oxidase in human diabetic arteries. Protein kinase C inhibitors may have vasculoprotective effects in diabetic patients.

AORTIC DISSECTION

175 Seasonal variation in the risk of acute aortic dissections

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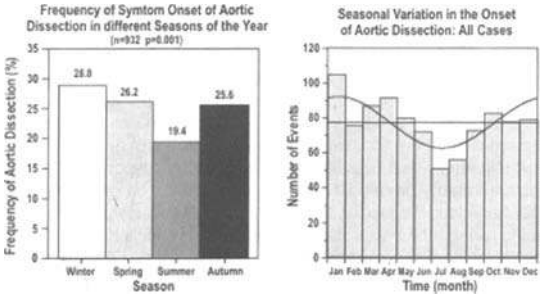
Background: Seasonal variations have been shown to influence the occurrence of a variety of cardiovascular disorders. However, the effects of circannual rhythms on the risk of acute aortic dissection (AAD) have not been studied.

Methods: To evaluate the impact of seasonal changes on the risk of AAD, we studied 957 patients enrolled in the International Registry of Acute Aortic Dissection between 1996 and 2000 (mean age 62+14 years, type A 61%). For the purpose of seasonal analysis patients were grouped according to their symptom onset during the four seasons (winter = December 21st through March 20th, spring = March 21st through June 20th, summer = June 21st through September 20th, and autumn = September 21st through December 20th). Chi-square test for goodness of fit and partial Fourier analysis were employed to evaluate non-uniformity and rhythmicity, respectively, of AAD during various seasonal periods.



Results: A significant seasonal variation occurred in the frequency of AAD with maximum incidence in winter (chi-square=17.5, d.f=3, p=0.001, Figure-left panel). The winter peak was significantly higher compared to the other 3 seasons (chi-square=7.0, d.f=1, p=0.008). Fourier analysis identified a peak incidence of AAD in the month of January (95% confidence limit January-February, p=0.022; Figure-right panel).

Conclusions: Similar to other cardiovascular conditions, AAD exhibits significant seasonal variations with highest incidence in winter. Our findings may have important implications for the prevention of AAD by tailoring treatment strategies to ensure maximal benefits during the vulnerable period.

176 Variable seasonal peaks for different types of aortic dissection?

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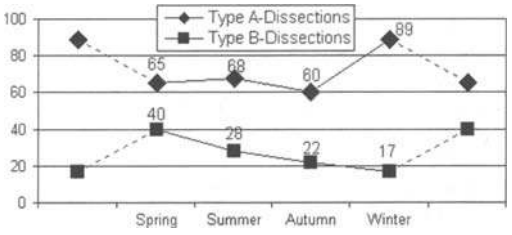
Background: Daily clinical practice suggests seasonal variability in the occurrence of aortic dissection.

Methods: We reviewed all records of patients admitted to our hospital for acute dissection from autumn 1990 to summer 2001. The screening and confirmation of the diagnosis of acute aortic dissection was performed exclusively by transesophageal echocardiography.

Results: Within the investigated eleven years' period, acute aortic dissection was diagnosed in 389 patients. In 282 patients acute Stanford type A aortic dissection was found and 107 patients had Stanford type B aortic dissection. Cyclic variation regarding the incidence of the different types of acute aortic dissection throughout the year was analysed by dividing the year into its four seasons of equal length. Each season was compared with the rest of the year using Chi-Square test with Bonferroni-correction (significance for p-values < 0.0125). In type A aortic dissection a significant peak of 89 cases in winter versus 65 in spring, 68 in summer and 60 in autumn was found (p = 0.011, figure). Conversely, in type B aortic dissection, there was a peak incidence in spring with 40 cases versus 28 in summer, 22 in autumn and 17 in winter (p = 0.003, figure).



Number of aortic dissections by season.

Conclusion: The underlying factors for the observed seasonal differences regarding both, type A and type B dissections, are not well understood, but the pattern of type A dissection resembles that of cyclic arterial blood pressure variation, which exhibits a seasonal peak in the coldest season. This is of relevance as hypertension is likely to be one of the most important predisposing factors of aortic dissection. Seasonal changes of blood pressure, however, do not explain the higher rate of type B dissections in spring.

177 Up to 7 years experience with valve sparing aortic root reconstruction (remodelling/reimplantation) for acute type A dissection

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Purpose: The operative strategy for treatment of type A dissection remains a major challenge especially if the aortic leaflets are macroscopically intact. Valve preserving techniques are theoretically attractive but require extensive longer-term evaluation for final judgment of these operative techniques. We present our results with two types of valve sparing techniques: the remodeling method according to Yacoub (group 1) in comparison to the reimplantation technique according to David (group 2).
Methods: Between October 1994 and November 2001, 134 patients were operated for acute type A dissection. Among those were n=21 in group 1 (remodeling) and n=15 in group 2 (reimplantation). Age in group 1 was 60±14 and 54±12 years in group 2 (p=0.11). Bypass time was 209 minutes (median) in group 1 versus 212 minutes in group 2 (p=0.62). The number of patients with cardiogenic shock at admission were 6 (26%) and 9 (60%) in groups 1 and 2, respectively (p=0.09). Patients were followed echocardiographically and clinically for up to 55 (median 25) months in group 1 and up to 87 (median 9) months in group 2 (p=0.47).
Results: Hospital mortality was 19% (n=4, group 1) and 20% (n=3, group 2; p=1.0). The only factor significantly associated with hospital mortality was cardiogenic shock on admission (p=0.013). There were 5 (24%, 1 cardiac related) and 1 (8%) late deaths in groups 1 and 2, respectively (p=0.35). Overall survival was 57% at 55 month for group 1 and 73% at 87 month for group 2. In group 1, reoperation due to re-dissection of the aortic root was necessary in 3 patients. In these 3 patients, Glutaraldehyde Resorcin Formalin [GFR] glue was used intraoperatively (p=0.019 as compared with the non-use of GFR glue), and 2 patients had Marfans disease (p<0.001 as compared to patients without Marfans disease). There were no reoperations for re-dissection of the aortic root in group 2 (p=0.28). Echoardiographic results were as follows: aortic regurgitation ≤I° in all patients; the mean pressure gradient across the left ventricular outflow tract was 3.0±1.5 in group 1 and 3.5±1.1 mm Hg in group 2 (p=0.51); the ejection fraction was 56±13 and 68±6% in groups 1 and 2, respectively (p=0.037).
Conclusion: Valve preserving techniques for type A dissection provide encouraging hemodynamic results. The reimplantation technique in this situation seems durable and preferable especially for patients with Marfans disease or when GFR glue is needed. The major risk factor for hospital mortality (cardiogenic shock on admission) requires further attention.

178 Dissection of descending aorta in Marfan syndrome

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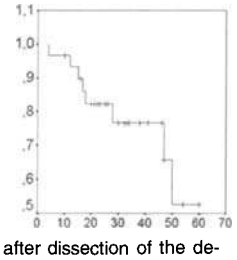
Prevalence and natural history of dissection (diss) of the descending aorta (Ao) is not well documented.
1250 patients came to our out-patient clinic dedicated to Marfan syndrome (MFS), mean age 29±15, 215 (51%) females. MFS was diagnosed according to international criteria, with the collaboration of a cardiologist, an ophthalmologist, a pediatrician, a rheumatologist and a genetician. Siblings were invited to come.
Out of 415 MFS patients, diss of the descending Ao occurred in 30 (7,2%); mean age 42±11 yo, 13 (43%) females. Mean follow-up was 3.3±2.5 years after dissection. Diss of the descending Ao was an extension of a diss of the ascending Ao in 27 patients. In only 3 MFS diss was localized only to the descending Ao.
MFS was recognized before diss in 7 patients (23%) who were receiving a beta-blocker (B-). After dissection, 24 patients (80%) received B-; Out of the 6 patients not receiving B-, 2 received calcium antagonist, one ACEI, and 3 no treatment (2 unwilling to take therapy, and one stopped because of side effects).
No diss occurred during pregnancy, but 2 early after delivery (4 days and 8 days). Six patients underwent surgery on the descending Ao: one at the time of diss, and 2.3, 3.4, 4.3, 4.8, 7.1 years after the acute event (mean 4.4 years). 4 patients deceased (1.5, 2.3, 4.2, 9.8 years after dissection; mean 4.5 years). Figure 1 shows the event free survival curve in our patients, for the 60 first months after diss.



Conclusion: dissection of the descending Ao is usually an extension of a dissection of the ascending Ao in MFS. The event-free survival curve after dissection of the descending Ao strongly supports operation before dissection of the ascending Ao occurs.

179 Aortic complication during and after pregnancy in Marfan syndrome

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Pregnancy has been associated with an increased risk of aortic dissection and dilation in women with Marfan syndrome (MFS)
We set up a multidisciplinary out-patient clinic devoted to Marfan syndrome gathering an ophthalmologist, a cardiologist, a pediatrician, a rheumatologist and a genetician.
1450 patients came to this clinic. MFS was diagnosed according to international criteria in 450 MFS including 154 women above 18 y.o.. Eighty six MFS women had 130 children.
MFS was recognised before pregnancy in 11 women who received beta-blocker during pregnancy. No complications occurred.
Aortic surgery was performed in 24 women having children and 13 having no children. However, aortic surgery had to be performed only 4 times during pregnancy for aortic dissection (n=4) and once 4 days after delivery for aortic dilation.
If only women having children younger than 40 are considered (n=45), mean age is 32, i.e. identical to that of women without children. Twelve had been operated on (i.e.27%), compared with 13 of the 68 having no children (i.e. 19%) (p=NS).

Women with and without children

	Women with children	Women without children
Number	86	68
Age	42±12	32±12
Age for pregnancy	25.7	
Aortic dissection	14 (16.3%)	9 (13.2%)
Surgery for aortic dilation	10 (11.6%)	4 (5.9%)
Surgery for aortic diss or dil	24 (28%)	13 (19%)
Mitral surgery	5 (5.8%)	6 (8.8%)

Conclusion: In our group of 86 women with MF syndrome having had pregnancy, 1) underdiagnosis was frequent, 2) few aortic surgery had to be performed during pregnancy, and 3) the rate of aortic complication was not significantly higher in women having children

180 Early and long-term results of total aortic arch grafting in elderly patients

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Improved techniques of surgical management have progressively reduced the risk of aortic surgery. Moreover, the proportion of aortic aneurysm increases in elderly. As a result, an increasing number of patients over 70 undergo total aortic arch grafting. On the other hand, perioperative cerebral complications cause of poor outcome. This study assesses our experiences with aortic arch grafting using a refined cerebral protection comparatively between elderly and younger patients.
Patient and methods Of 101 consecutive patients underwent aortic arch grafting from June 1994 to January 2002, 37 patients were 70 years or older. Mean age at the time of surgery was 73.4 ± 2.8 years. Aneurysms were atherosclerotic in 25 and aortic dissection in 12. Nine patients were in states of shock preoperatively. The control group consisted of 64 patients under 70 years. There were no significant difference of preoperative conditions between both groups. We conducted total arch grafting using hypothermic antegrade selective cerebral perfusion to every aortic arch branch. Carbon dioxide gas was added to the cerebral perfusion in order to inhibit the increase in the cerebral vascular resistance during hypothermic cerebral perfusion.
Result Hospital mortality was 8.1% in the elder group and 4.7% in the younger group (p=0.49). No operative major cerebral complications were observed, although 4 patients in the younger group experienced temporary neurological symptoms. The rate of postoperative respiratory problems was higher in the elder group (p=0.026). The mean length of postoperative ICU stay was longer in the elder group (p=0.049). The mean length of postoperative hospital stay was not significant different between both group (31.9 days in the elderly and 29.9 days in the younger). The seven year survival was 61.6 ± 10.6% in the elder group and 79.8 ± 5.6% in the younger group (p=0.38). Freedom from aortic events (re-operation, rupture and cholesterol embolism) after 7 years was 88.4 ± 6.4% in the elder group and 70.1 ± 10.5% in the younger group (p=0.66).
Conclusion Early and long-term results of total aortic arch grafting using integrated antegrade cerebral perfusion in patients older than 70 years were satisfactory compared with those of patients under 70 years of age.

LESION SEVERITY: OUR EYES ARE NOT GOOD ENOUGH!

185 Invasive assessment of intermediate coronary stenosis – comparison of intracoronary ultrasound with fractional flow reserve

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Background: Intracoronary ultrasound (ICUS) derived minimal lumen cross-sectional area (LAmin, mm^2) <4.0 is used as the cut-off value for revascularization in patient with intermediate coronary lesion (IML). Pressure-derived fractional flow reserve (FFR) <0.75 is strongly related to provokable myocardial ischemia. The aim of the study was to evaluate the usefulness of ICUS assessment of IML in comparison to FFR.
Methods: In 56 pts with stable angina and IML (Diameter stenosis (DS) =40-60% by QCA), without left main stenosis, prior myocardial infarction or left ventricular hypertrophy, FFR was calculated after intracoronary injection of adenosine (40-80 μg for the left coronary artery, 15-30 μg for the right). Than, in all lesions ICUS was performed using automated pull-back (0.5 mm/sec) to calculate LAmin and the lesion length (LL, mm). According to FFR pts were divided into two groups: Group 1: FFR<0.75 (12 pts), Group 2: FFR>0.75 (44 pts). All lesions with FFR>0,75 were not revascularized and followed-up for 12 months to assess the frequency of lesion-related major adverse cardiac events LR-MACE (death, myocardial infarction, target lesion revasularization).
Results: The comparison of QCA, FFR and ICUS parameters between the two groups is shown in table. LAmin>4.0 was obtained in 3 pts (25%) in group 1, and LAmin<0.4 was present in 16 pts (36%) in group 2. There was no LR-MACE during 12 months follow-up among patients with LAmin<4.0 and FFR>0,75.

	Ref.D-QCA	LL-QCA	MLD-QCA	DS-QCA	FFR	LAmin-ICUS	LL-ICUS
Group 1	3.02±0.54	18.3±5.8	1.50±0.17	49.7±7.0	0.67±0.08	3.20±0.45	19.5±7.14
Group 2	3.06±0.38	11.3±3.9	1.48±0.27	51.8±7.8	0.85±0.05	3.74±1.01	11.2±5.13
p=	NS	0.018	NS	NS	0.0027	0.042	0.0017

Conclusions: ICUS assessment of the minimal lumen cross-sectional area has only a limited value in determining the clinical importance of intermediate coronary lesion. Lesion length influence functional severity of intermediate coronary lesion. Even in patients with LAmin<4.0 deferral of intervention based on FFR is safe and associated with good long-term clinical outcome.

186 The angiographical stenotic flow reserve compared to intracoronary haemodynamic parameters for evaluation of coronary lesion severity

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Background: Based on fluid dynamics equations and the geometry of coronary narrowings, quantitative coronary angiography (QCA) provides an estimate of coronary flow reserve (the stenotic flow reserve, SFR).
Objective: A direct comparison between stenotic flow reserve and intracoronary-derived coronary flow reserve parameters (fractional flow reserve (FFR), coronary flow velocity reserve (CFVR) and relative coronary flow velocity reserve (rCFVR)), for functional evaluation of coronary lesion severity as determined by 99mTc MIBI-SPECT as substudy of the ILIAS study (Intermediate Lesions: Intracoronary-flow Assessment vs. 99mTc MIBI-SPECT).
Methods: A total of 201 patients with stable (CCS class 1-3) or unstable (Braunwald class I-II) angina underwent myocardial perfusion scintigraphy in a two day stress-rest protocol to determine reversible perfusion defects.
Quantitative coronary angiography was performed using the CMS-QCA software 3.32 (MEDIS, Leiden, the Netherlands) which includes the analysis of stenotic flow reserve.
FFR, CFVR and rCFVR (defined as the ratio of CFVR of the narrowed vessel and CFVR of the reference coronary artery) were determined with guide wires distal to 163 coronary lesions (mean diameter stenosis of 57%; range 20%-87%), during baseline and maximum hyperemia (induced by 15-20 mcg adenosine ic).
Linear regression was performed to determine the relationship between stenotic flow reserve and FFR, CFVR and rCFVR.
ROC-analysis was performed to determine the best cut off value of stenotic flow reserve and the predictive values of stenotic flow reserve, FFR, CFVR, rCFVR for detection of reversible perfusion defects (by area under curve, AUC).
Results: Linear regression showed moderate relations between stenotic flow reserve and FFR (r=0.64, p<0.0001), CFVR (r=0.51, p<0.0001) and rCFVR (r=0.60, p<0.0001). The area under the curve of stenotic flow reserve was 0.75±0,05 with a best cut-off value of 2.25. The area under the curve of FFR, CFVR and rCFVR was 0,79 ± 0,05, 0,76 ± 0,04, 0,75 ± 0,03 respectively.
Conclusion: Stenotic flow reserve has a moderate agreement with fractional, absolute and relative flow reserve, while the predictive value of stenotic flow reserve for the functional evaluation of coronary lesion severity is similar to the intracoronary derived hemodynamic parameters.

187 The effect of lesion length on the functional significance of coronary lesions

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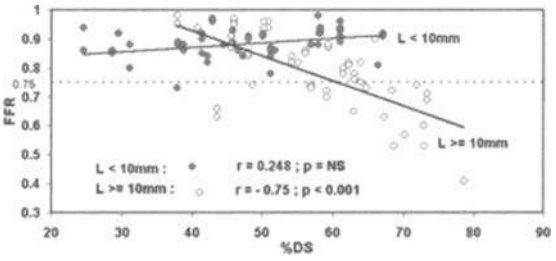
Background: Fractional flow reserve (FFR) has become the gold standard in physiologic assessment of coronary artery stenosis. This especially holds true for the functional evaluation of angiographically intermediate lesions. An FFR value < 0.75 is considered a reliable physiologic parameter indicating a functionally significant lesion. However, the effect of lesion length (LL) on FFR has not been adequately assessed. The current study was designed to examine the effect of LL on FFR in patients with coronary artery disease.
Methods: We performed FFR measurements by pressure guidewire, in 54 lesions (48 pts.). LL and percent diameter stenosis (%DS) at the lesion site were determined by performing quantitative coronary angiography (QCA) analysis.
Results: Overall, there was a moderate inverse correlation between FFR and %DS (r = -0.55, p < 0.001). Using a receiver operating characteristic (ROC) curve analysis, a LL = 10 mm was identified to be the best cutoff value for predicting a FFR < 0.75 (sensitivity 96%, specificity 63%, positive predictive power 40%, negative predictive power 98%). The correlation between FFR and %DS significantly improved for LL ≥ 10 mm, as compared to LL < 10 mm (r = -0.75, p < 0.001; r = 0.25, p = NS; respectively; Figure). Similar improvement with LL was observed for angiographically intermediate lesions (%DS: 50-70%: r = -0.73, p < 0.001 for LL ≥ 10 mm; r = 0.28, p = NS for LL < 10 mm).



LL effect on lesion functional severity.

Conclusions: This study demonstrates that lesion length differentially effects the correlation between the functional assessment (FFR) and the "anatomical" angiographic assessment (%DS) of coronary lesions and suggests that, lesion length has a significant impact on the physiologic significance of coronary artery lesions.

188 Intracoronary or intravenous adenosine during fractional flow reserve: influence of stenosis severity, collateral steal and branch order

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Background: Achievement of maximal vasodilatation of coronary microcirculation is a pre-requisite for performance of fractional flow reserve (FFR), a pressure derived index of coronary reserve. Although intravenous (iv) adenosine infusion has been proposed as the method of choice, intracoronary (ic) bolus administration in widely used in clinical practice. Little information is available, however, on the validity of the latter approach, and on adequate ic adenosine dosage.
Methods: Following a prospective study design, in 38 coronary stenosis with intermediate severity (54.2 ± 0.49) FFR was measured during coronary hyperemia induced with adenosine administered intravenously (140μg/kg/min) (FFRiv) and intracoronarily (incremental dosages of 20, 40 and 80μg) (FFRic). The discrepancy between FFRic and FFRiv measurements was estimated as the ratio FFRic/FFRiv. In 19 cases followed by PTCA, collateral flow index (CFI), defined as coronary wedge pressure/aortic pressure, was measured with (CFI-aden) and without concomitant iv adenosine infusion for one minute. Coronary steal was defined as the ratio CFI/CFI-aden. The influence of branch order, stenosis severity, CFI and coronary steal on the discrepancy FFRic/FFRiv was estimated.
Results: There were no adverse events in relationship with adenosine administration. Table I shows FFR data resulting from the different adenosine dosages

	20μg bolus	40μg bolus	80μg bolus	IV 140μg/kg/min
FFR	0.73 ± 0.15	0.72 ± 0.71	0.71 ± 0.20	0.68 ± 0.16
FFR<0.75 (%)	16 (42)	19 (50)	20 (53)	24 (63)
False negatives	8 (21.0%)	5 (13.1%)	4(10.5%)	0 (0%)
FFRic/FFRiv	1.09 ± 1.1	1.07 ± 0.8	1.05± 0.78	—

The discrepancy FFRic/FFRiv was not influenced by branching order (1.73±0.56), CFI (0.15±0.08) and coronary steal (1.23±0.35), but increased with stenosis severity (r=0.66, p=<0.0001), even after adjustment to FFRiv (r=0.68, beta coeff=0.49, p=<0.0001).
Conclusions: 1/ When compared with FFRiv an unacceptable high number of false negative FFRic readings occur even with dosages of 80 μg; 2/ the discrepancy between FFRic and FFRiv was not due to collateral steal; 3/ stenosis severity, on the contrary, increases the discrepancy between FFRic and FFRiv, presumably due to preferential washout of ic adenosine to side branches with less epicardial resistance.

189 Calculation of pressure-derived fractional flow reserve in patients with moderate left main coronary artery stenosis

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Background: Intracoronary ultrasound (ICUS) is widely used to define clinical significance of borderline left main stenosis (BLM). ICUS-derived: minimal lumen cross-sectional area (LAmin, mm^2) >9.0 and minimal lumen diameter (MLD, mm) >3,0 are proposed as the cut-off values for deferral revascularisation in patients with BLM. Pressure-derived fractional flow reserve (FFR) <0.75 is strongly related to provokable myocardial ischemia. However the application of FFR in patients with BLM was not clearly established. The aim of the study was to evaluate the usefulness of FFR assessment of BLM in comparison to ICUS.
Methods: In 21 pts with isolated BLM, without prior myocardial infarction or left ventricular hypertrophy, FFR was calculated before and after 1, 2 and 3 min of continuous intravenous infusion of adenosine (140 μg/kg/min). Than, in all lesions ICUS was performed using automated pull-back (0.5 mm/sec) to calculate left main LAmin and MLD. According to FFR pts were divided into two groups: Group 1: FFR<0.75 (6 pts), Group 2: FFR>0.75 (15 pts). Results: There was no complications occurring during invasive assessment of BLM. Angiographic percent diameter stenosis (assessed by QCA) was similar in both groups (group 1 vs. group 2: 41±3% vs. 45±6%, p=NS). ICUS-derived LAmin <9.0 and MLD <3,0 was present in all pts in group 1 and only in 2 pts (12%) in group 2. There was a strong positive correlation between FFR and LAmin (r=0,92, p<0,01).
Conclusions: Calculation of pressure-derived fractional flow reserve during intravenous administration of adenosine is safe and useful for the assessment of functional severity of borderline left main stenosis. There is a strong correlation between FFR and ICUS-derived left main minimal lumen cross sectional area.

190 Long-term clinical follow-up after treatment decision concerning an intermediate lesion in patients with multivessel disease

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Background: Assessment of functional significance of intermediate coronary narrowings is important for clinical decision making. In the ILIAS multicenter study we investigated the long term prognostic value of intracoronary derived Doppler flow velocity compared to the results of myocardial perfusion scintigraphy (MPS) for patient management of intermediate lesions.
Methods: A total of 191 patients (mean age: 61 years; male: 70%) with stable angina (CCS 2-3) and multivessel disease were included. Patients were referred for angioplasty of a severe lesion in the presence of an intermediate coronary lesion (40-70% diameter stenosis) in another coronary artery. MPS was performed in all patients to determine the presence of reversible perfusion defects in the area of the intermediate lesion. MPS was considered 'positive' when no reversible defect was present in this area. At angiography, in all patients the coronary flow velocity reserve (CFVR) was determined distal to the intermediate lesion. CFVR < 2.0 was considered 'positive'. Next to angioplasty of the severe lesion, angioplasty of the intermediate lesion was only performed if both MPS and CFVR were positive. Long term follow up (>1 year) was performed to document the occurrence of any major cardiac events (PTCA, CABG, myocardial infarction, death). The relative risk was calculated for MPS an for CFVR to predict future events.
Results: The mean percentage diameter stenosis of the intermediate lesion, as measured with quantitative coronary angiography, was 55% (range 35-74%). In 9 (5%) patients, the intermediate lesion was treated with angioplasty based on the results of MPS and CFVR. The mean follow up time was 793 days (range: 360-1525). In total 67 events occurred in 49 patients (3 deaths, 9 myocardial infarctions, 8 CABGs, 47 PTCAs). The mean time to the first event was 273 days (range: 2-1205). The eventrate was 33% (10/30) for patients with a negative, and 35% (57/161) with a positive test result on MPS. On the contrary, the eventrate was 24% (35/145) for patients with CFVR≥2.0, and 70% (32/46) for CFVR<2.0. Thus, the relative risk for was 0.9 (95% CI: 0.5-1.6) for MPS and 2.9 (95% CI: 2.0-4.1) for CFVR. This difference in relative risk was statistically significant (p<0.05).
Conclusion: Selective evaluation of an intermediate lesion using CFVR allows a more adequate risk stratification in patients with multivessel disease than MPS. A CFVR<2.0 was associated a three fold increase of the occurrence of cardiac events during long term follow up (mean of 2 year).

ANY PROGRESS ON CORONARY FLOW AND MYOCARDIAL PERFUSION?

191 Noninvasive measurement of regional subendocardial and subepicardial blood flow in normal humans

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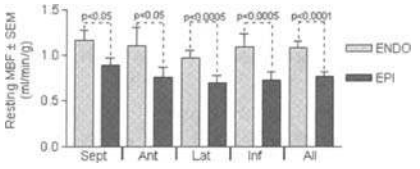
Introduction: Ischaemia is more severe in the subendocardial (ENDO) than subepicardial (EPI) layer in animal studies. Technical limitations have prevented the measurement of blood flow (MBF) in these layers in normal humans. We report the first measurements of absolute ENDO and EPI MBF in normal humans using a high sensitivity PET scanner.
Methods: A 3D PET scanner (EXACT3D), using oxygen-15 water, was employed to measure MBF at rest in 11 healthy volunteers (age 49±4) and during dobutamine induced stress in a subset of 7. At analysis the left ventricular wall was divided into equal inner (ENDO) and outer (EPI) halves and MBF measured in septal, anterior, lateral, and inferior regions. The oxygen-15 water kinetic was fitted to a model corrected for spillover from both ventricular cavities, surrounding tissue and for partial volume. MBF is expressed as ml/min/g of perfusable tissue.
Result: Heart rate and blood pressure were 57±10b/min and 116/69mmHg at rest and 105±29b/min and 138/69mmHg during stress respectively (mean maximum dobutamine dose 36±5μg/kg/min). Mean ENDO MBF for the whole heart was 1.1±0.5ml/min/g while EPI was 0.8±0.3ml/min/g ($p<0.0001$), with an ENDO/EPI ratio of 1.5. Resting ENDO MBF was significantly higher than EPI in each of the 4 regions. Stress ENDO and EPI MBF were 2.3±0.7ml/min/g and 2.2±0.7ml/min/g respectively for the whole heart (p=ns) resulting in a ratio of 1.1.



Regional and global ENDO & EPI MBF.

Conclusion: These results show that, as in experimental studies, human resting ENDO MBF is higher than EPI MBF at rest and that there is no regional variation in this relationship. The neural and autoregulatory mechanisms that control this distribution are affected by metabolic vasodilatation and, in normal subjects, transmural MBF distribution becomes uniform during stress.

192 Pulse transmission coefficient – a non-hyperemic index for physiologic assessment of procedural success after percutaneous coronary interventions

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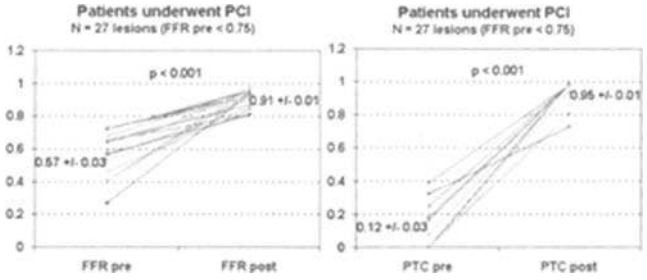
Background: Coronary lesions may impair the transmission of pressure waves across a stenosis, potentially acting as a high-frequency filter. The pulse transmission coefficient (PTC) is a novel non-hyperemic parameter that calculates the transmission of high frequency components of the pressure signal through a stenosis. Recently, it has been shown that PTC is highly correlated with fractional flow reserve (FFR) and a cutoff value of PTC <0.6 may predict an FFR <0.75 with high accuracy. Thus, it may apply as a surrogate index for FFR to reflect the physiologic severity of the coronary artery stenosis. This study was designed to study the change in PTC as compared to FFR, following percutaneous coronary intervention (PCI).
Methods: Pressure signals were obtained by pressure guidewire in 27 lesions (27 pts.) pre and post PCI, and were analyzed with a new algorithm (Florence Medical Ltd.) that identifies the high frequency component in the pressure signal. The PTC was calculated as the ratio between distal and proximal high frequency components of the pressure waveform across the lesion. FFR measurements were assessed with intracoronary adenosine.
Results: There was a significant increase in PTC following PCI (0.12 ± 0.03 at baseline to 0.95 ± 0.01 post PCI; p <0.001; Figure). Comparable changes were observed for FFR (0.57 ± 0.03 at baseline to 0.91 ± 0.01 post PCI; p <0.001).
Conclusions: Pulse transmission coefficient is a novel non-hyperemic parameter for physiologic assessment of coronary artery stenoses. Similarly to FFR, pulse transmission coefficient is significantly increased following PCI. Thus, it may serve as an adjunct index for the functional assessment of procedural success following PCI, especially in patients with impaired maximal hyperemia.



The change in PTC vs. FFR following PCI.

193 Coronary stenosis haemodynamics evaluated with a novel dual-sensor wire combining pressure and flow velocity signals

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Background: The lack of high fidelity simultaneous measurements of pressure and velocity distal to a stenosis has hampered the study of stenosis pressure drop-velocity (delP-V) relationships in patients.
Methods: Prototypes of a novel 0.014" dual-sensor guide wire, equipped with both a pressure and velocity sensor, were successfully used in 8 patients with a single stenosis to obtain per beat averages of delP and V from baseline to maximum hyperemia after an i.c. bolus of adenosine. DelP-V relations were constructed before PCI (pre), after balloon dilatation (PTCA) and after placement of a stent and/or upsized stent (UPstent) guided by intravascular ultrasound. Incremental changes in hemodynamics for each PCI step were compared (paired Students t-test) for fractional and coronary flow velocity reserve (FFR and CFVR) and for stenosis resistance index (SRv) calculated as delP/V at maximal hyperemia.
Results: In 4 out of 8 patients, the delP-V relations of the pre-PCI stenosis exhibited flow-limiting behavior (Figure 1) indicative of a compliant stenosis, which was stabilized by PTCA and stent. Dilation and stent placement reduced the lesion induced velocity-dependent delP, with an initial marked reduction in hyperemic delP and subsequent substantial gain in velocity (dotted line in Figure 1). Average percent incremental hemodynamic changes were highest for SRv (56.2% ± 36.7%) compared to CFVR (28.9% ± 29.6%, $p<0.01$) and FFR (14.7% ± 13.8%, $p<0.0001$).

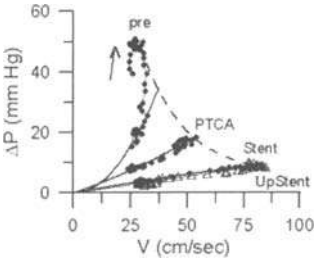

Fig.1: Effect of PCI on delP-V relations.

Conclusion: The hemodynamics of a coronary stenosis before and after each step of PCI is clearly defined by delP-V relations. SRv is a powerful and sensitive descriptor of the functional gain achieved by PCI, since it combines both pressure and velocity, which are affected to variable degrees by PCI.

194 The combination of hypercholesterolemia and hypertension augments alteration in myocardial microvascular architecture

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Background: Co-existence of the cardiovascular risk factors hypercholesterolemia (HC) and hypertension (HT) is associated with increased incidence of cardiac events. Both conditions are pro-inflammatory, and impair myocardial microvascular (μV) function. HC also leads to sub-endocardial neovascularization, but it is unknown if HT imposes a synergistic effect. We tested the hypothesis that early concurrent HC+HT increase μV spatial density more than each risk factor alone. Methods. Pigs were euthanized 12 weeks after either a normal (n=6) or HC (n=8) diet, renovascular HT (n=7), or both HC and HT (HC+HT; n=7). Myocardial samples of excised hearts were scanned using micro-computed tomography (micro-CT, 21μm-pixel resolution), and 3-D images reconstructed. Spatial density of small (<200μm) and large (200-500μm) μV was quantified in situ in the sub-epicardium and sub-endocardium. Results. Cholesterol levels were significantly and similarly elevated in HC and HC+HT (416±70 and 372±29 mg/dL, $p<0.001$ vs. normal and HT), while mean arterial pressure was similarly and significantly higher in HT and HC+HT (124±6 and 121±9 mmHg, $p<0.01$ vs. normal and HC). Left ventricular muscle mass (as measured by CT) was similar among all groups. The sub-endocardial spatial density (number/cm^2) of small μV was significantly and similarly increased in HC, HT, and HC+HT compared to normal (table, *$p<0.05$ vs. normal). However, the spatial density of small sub-epicardial μV was increased only in HC+HT. The spatial density of large μV was unchanged in either region.

	Normal	HC	HT	HC+HT
Sub-epicardium	743 ± 91	989 ± 162	909 ± 80	111 ± 76*
Sub-endocardium	736 ± 79	1170 ± 140*	915 ± 76	1116 ± 109*

Conclusions: Organ microvasculature structure can be accurately study with micro-CT. We show, for the first time, that early HC and HT each induce selective neovascularization of small μV in the sub-endocardium, while an interaction between HC and HT extends this to the sub-epicardium as well. Marked transmural alterations in myocardial μV architecture may impair regulation of myocardial perfusion, and may potentially be linked to myocardial ischemia in HC+HT.

195 Coronary terminal arteriole responses to changes in perfusion pressure: results from a new video microscopy approach to isolated hearts

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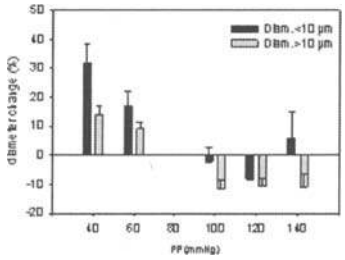
Introduction: To date, investigation of coronary arteriole vasomotor activity has been limited to arterioles > 30-40μm due to methodological problems. We now investigated responses of terminal arterioles to changes in perfusion pressure using a new microscopy technique in tetrodotoxin (TTX) arrested isolated hearts.

Methods: Isolated, rat hearts were perfused in a closed loop Langendorff system (filling volume 20 ml), which was placed on a computer-controlled microscope stage. Tilting of the microscope by 90° allowed access to the ventricular surface. A 20x objective was optically coupled to the heart by contact gel and a cover glass. The perfusate was stained with FITC-dextran, microscopic images were generated by a CCD-camera (Kappa CF8/1FMC), recorded on tape, and arteriole diameters were measured offline. After the onset of recirculation and a 30 min stabilization period, TTX (50μM) was added to arrest the heart and maintain oxygen demand at basal levels. Arterioles were identified by flow direction of fluorescent beads (1μm). Vasomotor responses of arterioles (< 25μm) to changes in perfusion pressure (PP: 60,40,100,120,140 mmHg) after baseline recordings at 80 mmHg were studied.

Results: % diameter changes of arterioles <10μm and >10μm from baseline PP are shown in the figure. Smallest arterioles (< 10μm) dilate more prominently at low PP, while larger arterioles show a more pronounced constriction at increased PP.



Conclusion: Consistent with transmural pressure distribution along the arteriolar tree, the pressure range for effective myogenic control is lower in the smallest arterioles than in upstream larger vessels. Thes data also confirm maintained vasomotor reactivity of coronary arterioles TTX arrested isolated hearts.

Supported by DFG Ha 1651/8-1Arteriole responses

196 Noninvasive assessment of coronary flow velocity in the everyday echo-laboratory practice. Experience on the first 1000 studies

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Coronary flow velocity reserve (CFVR) is a significant parameter to assess the coronary function; the possibility of its determination by a total noninvasive method will make its utilization more accessible and frequent. Objective. to evaluate the feasibility and value of measuring CFVR with transthoracic Doppler echocardiography (TTDE) in the daily practice. Methods. In 1000 consecutive patients (p) (635 male; mean age 64.9 ± 19 years) the diastolic coronary flow velocity was continuously monitored by pulsed- wave Doppler at the distal region of the left anterior descending artery (LAD), at rest and during the hyperemic phase induced by 0.84 mg/kg of Dipyridamole (Dip)for 4 min (803 p), 0.14mg/kg/min of Adenosine (Aden) for 2 min (103 p) or by the infusion up to 40 ug/kg/min of Dobutamine (Dob) (94 p). The test was performed in 323 p with angina, in 124 p with atypical chest pain, in 149 p during the post infarction period, in 32 p with dilated miocardiopathy, in 65 p after CABG, in 76 p following PTCA, in 61 p for preoperative risk evaluation, and in 170 p for others reasons. The CFVR was calculated as the ratio between the maximal and the basal velocity; these data were correlated with the angiograms performed the month after the TTDE in 209 p (Dip 164 p, Aden 28 p, Dob 17 p) Results. A clearly legible Doppler signal was obtained with Dip: 739/803 p, with Aden: 96/103 p and with Dob 66/94 p; the feasibility result was 92 %, 93% and 70% respectively. The results of group A (98 pts with LAD < 70% stenoses) were compared with group B (111 pts with LAD ≥ 70% lessions).

Group	pts (n)	BCFV(cm/seg)	MCFV (cm/seg)	CFVR
A: (LAD < 70%)	98	27.9 ± 8.7* *p = 0.008	65.7 ± 24 #	2.43 ± 0.8 " p < 0.0001 #"
B: (LAD ≥70%)	111	31.2 ± 12*	6.9 ± 19 #	1.5 ± 0.5 "

A CFVR ≥ 2 was registered in 72/98 p with non significant LAD lesions (specificity: 74%) and a CFVR< 2 was determined in 73/83 p with critical LAD stenoses (sensitivity of 88%).Conclusions. CFVR by TTDE has a high feasibility, especially with vasodilator drugs and renders a very useful noninvasive assessment of functionally significant disease in the territory of the LAD.

YOUNG INVESTIGATORS' AWARD SESSION (BASIC SCIENCE)

200 Human endothelial progenitor cells can transdifferentiate into functionally active cardiomyocytes

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Background: In addition to promoting angiogenesis, cell therapy may be an approach for cardiac regeneration. Embryonic stem cells can differentiate into cardiomyocytes in vitro and improve heart function in vivo. Recent studies suggest that committed progenitor cells can transdifferentiate into other lineages. However, the transdifferentiation potential of human endothelial progenitor cells (EPCs) is unknown.
Methods and Results: EPCs were obtained from peripheral blood mononuclear cells of healthy adult volunteers by cultivating with endothelial cell medium and growth factors. After 3 days, more than 95% of adherent cells were functionally (dil-ac-LDL-uptake) and phaenotypically (expression of VEGF-R2 and VE-cadherin) EPCs. EPCs were then co-cultivated with neonatal rat cardiomyocytes for 6 days. This lead to significant increases in cell length and size ($p<0.001$) of EPCs to a cardiomyocyte-like morphology. Biochemically, 11,8±2,3% of human EPCs (from n=7 healthy volunteers) expressed alpha-sarcomeric actinin as measured by flow cytometry. Immunocytochemistry showed that human EPC's expressed alpha-sarcomeric actinin, cardiac troponin I (both partly with sarcomeric organisation), ANP and MEF2. Fluo 4-imaging demonstrated calcium transients synchronised with adjacent rat cardiomyocytes in transdifferentiated human EPCs. Importantly, actively contracting human cardiomyocytes were identified. This transdifferentiation of EPCs into cardiomyocytes was not reproduced by conditioned medium, suggesting an important role of cell-to-cell contact. Single cell microinjection of lucifer yellow or labelling of cardiomyocytes with calcein-AM demonstrated gap junctional communication between 51±7% of EPCs (16 hours after labelling, n=4) and rat cardiomyocytes.
Conclusions: Adult human EPCs can transdifferentiate in vitro into functionally active cardiomyocytes when co-cultivated with rat cardiomyocytes. This was demonstrated by morphological, biochemical and functional parameters. The therapeutic use of autologous EPCs may aid cardiomyocyte regeneration in patients with ischaemic heart disease.

201 Beneficial effects of neonatal cardiomyocytes on left ventricular ejection fraction and scar thickness six months after transplantation into infarcted rat hearts

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Cardiac cell transplantation is a novel strategy to replace lost myocardium after myocardial infarction and improve cardiac function. However, the longer term effects of such treatment on myocardial dysfunction are not well known. Therefore, we tested the impact of neonatal cardiomyocytes on overall and regional cardiac contractility, left ventricular (LV) volumes and LV geometry 6 months after transplantation into infarcted hearts.
Isolated cardiomyocytes from male neonatal Fischer 344 rats (1-2 d, 3-5 x 10^6/50 µl) or medium were injected into the infarcts of adult syngeneic female animals 1 week after left coronary artery ligation. LV angiography 6 months after cell transplantation revealed a greater ejection fraction in treated animals than in control (0.36±0.03 vs. 0.25±0.02, both n=9, $p<0.01$). There was a trend for greater stroke volume (97±11 vs 71±9 µl, p=0.09) and smaller endsystolic volume (172±18 vs 215±21 µl, p=0.14), while enddiastolic volume was similar. Analysis of regional wall motion indicated that in cell treated rats 29.5±8.3% of the myocardial infarct zone was dyskinetic vs. 55.1±7.3% in control rats (p=0.035). Average chordal shortening within the myocardial infarct zone was positive in treated rats but negative in controls (p=0.02). LV hemodynamics (n=9 each) showed similar enddiastolic pressure, maximal systolic pressure and maximal rate of rise and fall of ventricular pressure (+dP/dt, -dP/dt). Post mortem analysis of LV geometry (hearts were fixed in distension with 10 mmHg intracavity pressure) revealed similar LV volumes and infarct sizes in the treated group as in control (0.42±0.02 vs. 0.45±0.03 ml and 31.5±1.7 vs. 34.2±2.8%). However, scar thickness was greater in treated animals (909±97 µm vs. 619±41 µm, $p<0.02$).
Previously, it was shown that neonatal cardiomyocytes survive in large number for at least 6 months after transplantation into infarcted hearts. Here, we found that these cells increase scar thickness and improve left ventricular ejection fraction and regional wall motion in vivo. These results support the hypothesis that cardiac cell transplantation provides a longer term benefit on LV function after myocardial infarction. Thus, cell transfer may become a meaningful therapeutic option to treat human heart disease.

202 Development of myocardial hibernation in mice is associated with chemokine induction and macrophage recruitment

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Brief repetitive ischemic events may have an important role in the pathogenesis of the ventricular dysfunction associated with myocardial hibernation. We have previously demonstrated that a single 15 min. episode of murine myocardial ischemia (I) followed by reperfusion (R) is associated with chemokine induction. We hypothesized that brief repetitive myocardial I/R may induce a persistent inflamatory reaction in the mouse heart, potentially leading to fibrosis and dysfunction in the absence of a completed infarction. C57/BL6 mice underwent daily 15 min. left anterior descending coronary occlusions followed by a reperfusion for intervals ranging from 3 to 28 days. The hearts of I/R and sham operated animals were evaluated with and processed for histology and RNA studies. M-mode echocardiography demonstrated a decreased fractional shortening in the I/R animals (sham 46.3±1.5%, 7 days I/R 35.2±2.5%, 28 days I/R 40.83±0.8%, both $P<0.05$; n=7) and regional dysfunction of the anterior left ventricular wall. Collagen staining using picrosirius red showed significant interstitial fibrosis after 7 days of I/R in the anterior left ventricular wall (sham vs. I/R: 4.6±2.0% vs. 21.5±6.5%, $P<0.05$; n=8), that remained unchanged for longer I/R protocols. Ischemic areas had no evidence of infarction, but demonstrated macrophages and fibroblasts accumulation after 3 to 7 days of I/R. A robust mRNA upregulation of the chemokines RNA MIP-1alpha, MIP-1beta, MIP-2 and MCP-1 was noted, peaking after 7 days of I/R and decreasing after 28 days. Mice undergoing 7 and 28 days of I/R followed by a 30 and a 60 day period of recovery, demonstrated a significant decrease in myocardial fibrosis (30 days 13.5±2.3%, 60 days 8.4±1.6%, $P<0.05$; n=8) and improved ventricular function. Brief repetitive I/R induces a murine ischemic cardiomyopathy with features of hibernation (reversible fibrosis and systolic dysfunction). Early chemokine induction may have a role in mediating the interstitial fibrosis and subsequent left ventricular dysfunction.

203 Atorvastatin decreases fas ligand expression and cytotoxicity in activated human T lymphocytes. Role of Rho proteins

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Background: HMG-CoA reductase inhibitors reduce cardiovascular mortality, though the mechanisms of action have not been completely elucidated. The presence of T cells and apoptotic cells (macrophages and vascular smooth muscle cells) in atherosclerotic plaques is well established, and it is the reduction of cellular content that is a marker of the plaque's vulnerability. One of the main mechanisms of cell death activation is the Fas-Fas ligand system.
Methods and Results: We have studied whether the HMG-CoA reductase inhibitor atorvastatin can regulate the expression of Fas ligand (FasL) and cytotoxicity in human T cells (Jurkat). Transfection studies and mRNA analysis demonstrated that activation of Jurkat cells with phorbol esters (PMA - 50 ng/mL) and ionomycin (0.5 µg/mL) increased FasL expression. This effect was prevented in a dose-dependent manner in the presence of atorvastatin (0.1-1 µM). Mevalonate (10-100 µM), and geranylgeranylpyrophospahte (1-5 µM), but not farnesylpyrophosphate (1-5 µM), prevented the effect of atorvastatin, indicating that protein geranylation is implicated in FasL expression. The C3-exotoxin (0.01-5 µg/mL), that selectively inactivates Rho proteins activation, also decreases FasL expression on activated T cells in a dose-dependent manner. Overexpression of constitutively active RhoA increased FasL promoter activity in Jurkat cells and dominant-negative RhoA decreased FasL promoter activity in activated cells, indicating that RhoA is implicated in FasL expression. In addition, treatment with atorvastatin decreased cytotoxic activity of activated Jurkat cells on FasL-sensitive cells.
Conclusions: Atorvastatin regulates FasL expression in T cells, probably due to the inhibition of RhoA prenylation. These results provide novel information by which atorvastatin may regulate the cytotoxic activity of T cells and the number of total cells in the atherosclerotic plaque. In conclusion, the effect of atorvastatin on T cell activation suggests a potential immunomodulator effect of this statin.

204 A cardiac nitric oxide synthase 1 regulates contraction and calcium fluxes – a novel mechanism in the autocrine control of cardiac function

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Evidence indicates that endogenous nitric oxide (NO) can modulate myocardial contractility, but the source of NO remains uncertain. We investigated the role of a neuronal type NO synthase (NOS1), recently localised to the cardiac sarcoplasmic reticulum, in the regulation of myocardial contraction.
Left ventricular (LV) contraction was assessed in-vivo using transthoracic echocardiography and invasive haemodynamic monitoring under isoflurane anaesthesia, and in vitro using field stimulation of isolated LV myocytes. Mice with NOS1 gene disruption (NOS1-/-) were compared with their littermate controls (NOS1+/+). In addition, we examined the effects of acute specific inhibition of NOS1 in myocytes with vinyl-L-N5-(1-imino-3-butenyl)-L-ornithine (L-VNIO, 500 μM).
LV dimensions and heart rate were not different in NOS1-/- mice. Specific NOS1 inhibition with L-VNIO or gene disruption of NOS1 enhanced cell shortening of isolated myocytes (% at 6hz NOS1-/- 10.7±0.9 vs NOS1+/+ 7.21±0.8, $p<0.05$). Similarly, LV ejection fraction was 0.54±0.03 in NOS1-/- vs 0.45±0.02 in NOS1+/+ ($p<0.05$). Although the maximum rate of LV relaxation (dP/dTmin) was not different in-vivo or in-vitro, the onset of relaxation was delayed (TR50 in myocytes at 6hz NOS1-/- 26.53±1.44 vs NOS1+/+ 21.27±1.31ms; $p<0.05$).
To investigate the mechanism of increased contraction, we estimated sarcoplasmic reticulum (SR) calcium load by integrating the Na-Ca exchange inward current in response to a ten second application of 10mM caffeine. Acute inhibition or gene disruption of NOS1 was associated with an increase in calcium content of the SR (NOS1-/- 0.78±0.04 vs NOS1+/+ 0.64±0.03pC/pF, $p<0.05$). In addition, we demonstrated that calcium current density was greater in NOS1-/- myocytes and following acute inhibition with L-VNIO (ICa density at 0mV NOS1-/- −11.4±0.5 vs NOS1+/+ -9.1±0.5pA/pF; $p<0.01$). Furthermore, the slow time constant of decay of ICa was increased in NOS1-/- (37.3±21.5) vs NOS1+/+ (26.9±1.6ms) suggesting that increased calcium influx through the sarcolemma may contribute to the greater SR load in NOS1-/- myocytes.
Taken together these findings indicate that NOS1 plays a previously unrecognised role in the autocrine regulation of myocardial function. Since both NOS1 gene transcription and biochemical activity are regulated by calcium, localisation of this enzyme to the SR membrane is consistent with a negative feedback role for NO in myocardial inotropy and intracellular calcium fluxes.

LIPID MODULATING THERAPY: BENEFITS AND DISAVANTAGES

205 Antioxidant effect of olive oil phenolic content in a randomized double-blind controlled clinical trial

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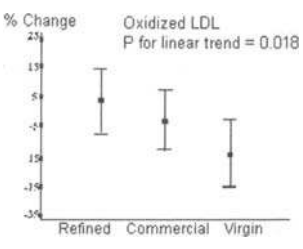
Background: The Mediterranean diet, in which olive oil is the main source of fat, has been shown to reduce the number of recurrences in patients with myocardial infarction. The aim of this study was to determine the effects of olive oil phenolic content on lipid peroxidation.
Methods: A placebo-controlled, double blind, cross-over, randomized, clinical supplementation trial using three olive oils with different phenolic compounds concentration (none, low and high), at moderate raw daily doses (25 ml/day), was conducted in 30 healthy non-smoking male volunteers. Olive oils were sequentially administered over three periods of 3 weeks preceded by two-week washout periods in which refined olive oil was used. Oxidized LDL, LDL resistance to oxidation (lag-time after Cu-oxidation) and antibodies against oxidized LDL (OLAB) were measured.
Results: A decrease in plasma oxidized LDL levels (linear trend, P= 0.018), and an increase in the LDL resistance to oxidation (linear trend, P=0.015) and a non-statistically significant decrease in OLAB were observed associated to the phenolic content of the olive oil administered (see figure). Urine tyrosol levels, as a marker of patient compliance, increased with the phenolic content of the olive oil consumed (linear trend, P= 0.020).



Conclusions: LDL is protected from oxidation by the phenolic content of olive oil, regardless of its MUFA and other antioxidant content. Our results show that regular consumption of a real-life daily dose of olive oil with high phenolic content is more effective protecting LDL from oxidation than that of olive oil with low or no phenolic content.

206 The effect of growth hormone replacement therapy on lipid profile, blood pressure and body composition in patients with hypopituitarism

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Growth hormone deficiency can increase cardiovascular mortality and morbidity, negatively affecting some risk factors, like lipid profile as known to predispose to coronary artery disease. The aim of this study was to investigate the effects of growth hormone replacement therapy (GHRT) on impaired lipid profile, blood pressure and body composition.
Method: Twenty patients (13 females, mean age: 51±6 years; 7 males, mean age: 46±13 years) who were followed-up at the Endocrinology Clinic due to hypopituitarism with no cardiac involvement (normal ECG, ECHO, and holter monitoring) were included in the study. The diagnosis was based on the insulin tolerance test. The patients, who were on the replacement therapy also for other pituitary hormone deficiencies, were planned to receive GHRT for 2 years in doses recommended by the Growth Hormone Society Workshop. Data from 20 patients, who received GHRT for 6 months were assessed in this study. At baseline, third and sixth months after GHRT, total cholesterol, triglycerides, HDL- and LDL- cholesterol and fasting blood glucose levels were measured; systolic and diastolic blood pressures, body mass index (BMI), waist-hip-ratio (WHR) were also evaluated.
Results: Before treatment, cardiological findings were normal in all patients. While BMI of the patients did not change during the treatment, WHR decreased significantly (1.008±0.1, 0.954±0.1, 0.943±0.1, p=0.0002). Blood pressures at baseline, were normal and remained so after the treatment. Total (291.6±19.8, 243.8±13.6, 238.3±18.8, p=0.009) and LDL-cholesterol levels (210.5±15.8, 151.4±9.8, 147.7±13.1, p=0.0001) dropped significantly. There was a significant increase in HDL levels (41.3±3.4, 53.5±3.2, 56.2±4.3, p=0.0008). Although triglycerides and fasting glucose levels showed an increasing tendency, the difference from baseline did not reach to a significant level ($p>0.05$).
Conclusion: With a 6-month of GHRT, an improvement in cardiovascular risk factors has been observed –an improvement in lipid profile and a decrease in abdominal obesity. However, it is questionable whether these favorable effects will continue in the long-term. Therefore, it is obvious that there is a need for long-term prospective studies with GHRT

207 Better influence of statin than of fibrate on novel risk factors in combined hyperlipidemia

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Besides dyslipidemia, hypertension, smoking, obesity, other so-called novel risk factors for coronary artery disease are playing increasingly important role as markers for the development and progression of atherosclerosis. Among them are C-reactive protein (CRP), homocysteine, and proteins involved in haemostasis and synthesized by endothelial cells (tissue factor pathway inhibitor (TFPI), plasminogen activator inhibitor (PAI-1) and tissue plasminogen activator (t-PA)). The effect of cerivastatin and fenofibrate on these parameters was investigated in otherwise healthy middle-aged males with combined hyperlipidemia.
Thirty-eight males, aged 49±5 years were randomised to 12 weeks treatment either with cerivastatin with a daily dose of 0.2 mg to 0.4 mg to achieve an LDL cholesterol goal of <3.0 mmol/l or with fenofibrate 250 mg daily. Fasting serum lipids, CRP, homocysteine, total and free TFPI, PAI-1 and t-PA antigen and activity were measured before and after treatment. The drugs exerted different influences on serum lipids. The decrease of total and LDL cholesterol was significantly greater after cerivastatin (p=0.03, p=0.0008, respectively), while the decrease of triglycerides and the increase of HDL cholesterol were significantly greater in patients receiving fenofibrate (p=0.05 for both). No change in homocysteine level was observed in the cerivastatin group, while in the fenofibrate group it increased significantly from 11.5±4.0 to 16.6±3.2 μmol/l ($p<0.0001$). The CRP level decreased significantly after both treatments, after cerivastatin, from 2.20 (0.90-4.70) to 0.80 (0.40-1.50) mg/l (p=0.001), and after fenofibrate, from 1.60 (1.10-3.30) to 1.10 (0.70-2.70) mg/l (p=0.03). The CRP decrease was significantly greater after cerivastatin (-49,5%) than after fenofibrate treatment (-29,8%) (p=0,04). The decrease of total and free TFPI was significant after cerivastatin (from 80.3±11.2 to 69.5±15.6 μg/l, p=0.005, and from 9.4±1.8 to to 8.0±2.1 μg/l, p=0.01, respectively), but not after fenofibrate. Neither drug affected t-PA antigen and activity while fenofibrate increased PAI-1 antigen (p=0.05) and activity (p=0.004).
Taken together, these data provide additional information on the antiatherogenic mechanisms of these hypolipemic drugs. Further prospective studies, with a larger number of patients are needed to answer the question if these differences, beside their effects on lipids, can explain the greater relative risk reduction in secondary prevention studies with statins, than with fibrates.

208 The efficacy of folate supplementation in fibrate-induced hyperhomocysteinemia

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Purpose: Recently published studies reported, that fibrates may induce hyperhomocysteinemia, as a side effect. In our study we aimed to assess whether this effect depends on concentrations of folate and B12 or on renal functions and whether may be prevented by folate supplementation.
Methods: 58 subjects with total cholesterol (TCHOL)>6mmol/l (m34, f24; mean age 54.0yrs), without any pharmacotherapy and/or other manifest disease, were included to an open, prospective, parallel-group study. After 2 month of diet treatment, subjects were randomly divided in to 2 groups- statins: 3 months fluvastatin 40mg, followed by 3months fluvastatin 80mg or fibrates: 3month micronised fenofibrate 200mg, followed by 3months fenofibrate+ folate 10mg.
Results (see table):

Fibrates: (n=26)	baseline	post-diet	fenofibrate	fenofibrate+folate
TCHOL [mmol/l]	6.82±0.12	6.77±0.14	5.94±0.28***	5.43±0.23
triglycerides [mmol/l]	1.99±0.25	2.02±0.22	1.37±0.16***	1.15±0.18
homocysteine [umol/l]	10.9±0.89	10.8±0.77	15.3±1.15****	10.9±0.56++++
folate [ng/ml]	7.20±0.73	7.36±0.58	7.28±0.74	18.1±0.55++++
B12 [pg/ml]	316±25.1	286±18.8	317±25.2	331±52.7
cystathin C [mg/l]	0.83±0.06	0.83±0.04	0.91±0.03	0.94±0.03
Statins: (n=32)	**baseline**	**post-diet**	**fluvastatin 40mg**	**fluvastatin 80mg**
TCHOL	6.99±0.16	7.12±0.17	5.99±0.14****	5.69±0.18
triglycerides	1.80±0.15	1.71±0.14	1.66±0.16	1.76±0.20
homocysteine	9.9±0.54	10.1±0.57	10.7±0.54	10.1±0.67
folate	7.94±1.08	7.17±0.43	7.37±0.42	8.94±0.69
B12	297±28.4	288±15.5	313±18.8**	306±23.4
cystathin C	0.81±0.02	0.82±0.06	0.91±0.03	0.82±0.06

Wilcoxons paired test: ****p<0.0001, ***p<0.001, **p<0.01 visit 2 vs visit 3; ++++p<0.0001 visit 3 vs visit 4

Conclusions: Treatment with fibrates was followed by a significant increase in homocysteine. This side effect seems to be independent from folate or B12 concentrations and also from cystathin C, a marker of renal functions. Concomitant folate supplementation is able to normalize this fibrate-induced hyperhomocysteinemia.
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209 Beneficial effects of statins on cardiac function in non-ischaemic heart failure

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Retrospective analyses of clinical trials show beneficial effects of statins on heart failure. Animal studies suggest cholesterol-independent improvement of cardiac function and reduction of hypertrophy and fibrosis.
Patients with non-ischemic dilatative cardiomyopathy (n=25) were randomized to cerivastatin 0.4 mg (statin) or placebo in a double-blind, prospective study. Inclusion criteria were stable heart failure NYHA II-IV defined as stable use of diuretics, angiographic exclusion of coronary artery disease, and established therapy with ACE-inhibitors and betablockers. The mean treatment duration was 16.2 weeks in the placebo-, and 15.4 weeks in the statin group. The left ventricular ejection fraction (EF) as quantitated by radionuclidventriculography was 43.8% before and 34.5% after placebo treatment. In the statin group, EF increased from 45.0 to 54.25% (p=0.34, 2-tailed T-test). In the placebo group, cardiac output decreased from 6.3 to 4.6 l/min (p<0.05), but remained unchanged under statin treatment (5.03 vs 4.76 l/min, p=0.8).
The maximal distance in the 6-min walking test increased from 270 m to 317 m under statin treatment (p<0.05), but did not change in the placebo treated patients. Corresponding to the EF, brain natriuretic peptide (BNP) decreased by 25% (p=0.14) and troponin T (TnT) decreased by 57% (p<0.05) in the statin- but not in the placebo group. Serum levels of plaminogen activator inhibitor 1(PAI) decreased in the statin group from 72 U/ml to 61 U/ml (p<0.05) but were unaltered with placebo treatment. Standardized questionaires showed improvement of quality of life (p<0.05), social activities (p=0.78) and daily activities (p<0.05) with statin treatment but not in the placebo group.
Statins improve left ventricular function and consecutively exercise capacity and quality of life in patients with non-ischemic heart failure suggesting a lipid-independent, non-vascular impact of statins on the diseased myocardium.

210 Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: 2-years follow-up by high-resolution MRI

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Background: The aim of this study was to investigate the effects of lipid-lowering by simvastatin on human atherosclerotic lesions. After the preliminary report we are now presenting the long-term follow-up results.
Method and patients: Eighteen asymptomatic hypercholesterolemic patients with documented aortic and/or carotid atherosclerotic plaques were selected for the study. A total of 35 aortic and 25 carotid artery plaques were detected. We performed sequential MRI of the aorta and carotid artery at baseline, at 6, 12, 18 and 24-months after lipid-lowering therapy with simvastatin. The effects of the treatment on atherosclerotic lesions were measured as changes in lumen area (LA), vessel wall thickness (VWT) and vessel wall area (VWA), a surrogate of atherosclerotic burden.
Results: Simvastatin induced a significant (P<0.01) reduction in total and LDL-cholesterol (-23%) and LDL-cholesterol (-38%) levels at 6-weeks and was maintained thereafter. At 6-months no changes in LA, VWT or VWA were observed. At 12-months significant (p<0.01) reductions in maximal VWT and VWA without changes in LA were observed: respectively -9% and -8% for aortic and -11% and -15% for carotid plaques. Further decrease in VWT and VWA was seen at 18 and 24-months of treatment (ranging from -15% to -25%). Surprisingly, at 24-months the LA showed a slight but significant increase (ranging 5 to 7%) for both carotid arteries and aortic lesions.
Conclusion: This long-term in vivo human study demonstrates that effective and maintained lipid-lowering therapy by simvastatin is associated with a significant regression of atherosclerotic lesions. Our observation suggests that initially statins induce vascular remodeling manifested by reduced atherosclerotic burden without changes in the lumen size. Long-term (>24 months) treatment of non-stenotic lesions may, however, results in an increase of luminal size.

EFFECTS OF NEW AND ESTABLISHED LIPID-LOWERING DRUGS

211 Effects of fluvastatin after successful percutaneous intervention in patients with CHD: the Lescol Intervention Prevention Study (LIPS)

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Background: Based on evidence from large clinical trials, statins are now well-established as the primary and secondary prevention of fatal and non-fatal coronary events. However, no study has prospectively evaluated the long-term effect of statins on clinical outcomes in patients who have undergone their first PCI, a well defined population at an early stage of disease.
Methods: LIPS is a double-blind, randomized trial designed to compare the effect of fluvastatin (40 mg bid) on major adverse cardiac event, ie MACE (cardiac death, non-fatal MI, repeat-CABG-or PCI)-free survival time in 1677 patients (844 fluvastatin; 833 placebo) with CHD and first successful TCT over a 3 year follow-up (median 3.98 y). Inclusion criteria were: ages 18–80 years; first successful TCT within 6 months before randomization; total cholesterol of 135 – 270 mg/dL (3.5 - 7.0 mmol/L) with fasting triglycerides <400 mg/dL (<4.5 mmol/L).
Results: Statistically significant treatment effect (p=0.0127; log-rank test) in first MACE free survival time was demonstrated for fluvastatin over placebo. For the primary endpoint, the incidence was 21.4% in the fluvastatin group vs 26.7% in the placebo group resulting in a 19.9% reduction in MACE events. Cardiac death occurred in 1.5% in the fluvastatin group and in 2.9% in placebo controls (p=0.0632; log-rank test). No significant difference in non-cardiac mortality was seen between groups (2.7% vs. 3.0% in fluvastatin and placebo, respectively).

Baseline characteristics

Mean age (y)	60.5 ± 10	Anginal status	(%)
Male (%)	84.0	Unstable	49.7
Smoking (%)	26.6	Stable	40.5
Body Mass Index (kg/m^2)	26.6 ± 3.3	Silent ischemia	9.8
Blood pressure (mm Hg)	128.0/75.0	Previous MI	44.3
Heart rate (bpm)	66.0 ± 11	Q-wave	26.8
Diabetes mellitus (%)	12.0	Non Q-wave	17.6
Total Number Of Lesions Treated	2222.0		

Summary: LIPS is the first study to investigate the effects of statin therapy on MACE in patients who have undergone successful primary TCT for CHD and has shown a significant benefit of fluvastatin in time to first event in this population. Final detailed results will be presented.

212 Comparing rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia

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This 6-week, randomized, double-blind trial (4522IL/0033) was conducted in hypercholesterolemic patients to compare the lipid-lowering effects of rosuvastatin (RSV, Crestor®) and atorvastatin (ATV, Lipitor®) across studied dose ranges. Patients with LDL-C ≥4.14 but <6.47 mmol/L (≥160 but <250 mg/dL) and fasting triglycerides <4.52 mmol/L (<400 mg/dL) received once-daily RSV 5, 10, 20, 40, or 80 mg (n=209) or ATV 10, 20, 40, or 80 mg (n=165). Mean percentage changes from baseline to wk 6 in lipid measures across the dose range for each drug were assessed by linear-regression analysis using analysis of covariance. The overall % reduction (from baseline) in LDL-C levels across the 10–80 mg dose range for RSV was –46.6% to –61.9% and for ATV was –38.2% to –53.5%, respectively. RSV (5–80 mg) was superior to ATV (10–80mg) at lowering LDL-C across the dose range (mean % change: –8.4%; P<0.001). RSV produced significantly (P<0.001) greater reductions than ATV across the dose range in total cholesterol (–4.9%), non-high-density lipoprotein cholesterol(non-HDL-C; –7.0%), apolipoprotein (apo) B (–6.3%), LDL-C:HDL-C (–9.5%), total cholesterol:HDL-C (–6.9%), non-HDL-C:HDL-C (–8.4%), and apo B:apo A-I (–7.8%). Dose responses for HDL-C, triglycerides, and apo A-I were not log-linear within each treatment or parallel between treatments; therefore, % changes between treatments were compared on a dose-by-dose basis using analysis of variance. Significant treatment differences were noted as follows: RSV 40 and 80 mg over ATV 40 and 80 mg in HDL-C (+12.3% vs +4.1% and +9.6% vs +2.1%; P<0.001 and P<0.01); ATV 80 mg over RSV 80 mg in triglycerides (–34.4% vs –19.7%; P<0.05; [median % change: –39.1% vs –24.7%]); and RSV 80 mg over ATV 80 mg in apo A-I (+9.2% vs +3.1%; P<0.05). Occurrences of treatment-emergent adverse events were similar between RSV and ATV; additionally, no clinically significant increases in hepatic transaminases or creatine kinases were observed with either trial medication. In summary, rosuvastatin was more effective than atorvastatin in reducing LDL-C across equivalent dose ranges; rosuvastatin was also more effective in decreasing total cholesterol, non-HDL-C, and apo B, improving lipoprotein ratios, and increasing HDL-C to a greater extent than atorvastatin. These findings suggest that the efficacy of a given rosuvastatin dose is at least equal to that of atorvastatin at twice the mg-equivalent dose. The enhanced lipid-altering effects of rosuvastatin should facilitate prompt attainment of lipid-treatment goals in clinical practice.

213 Addition of ezetimibe to ongoing statin therapy: incremental reduction in low-density lipoprotein cholesterol is independent of statin type

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Background: This randomized, double-blind, placebo-controlled study evaluated the lipid-altering efficacy of adding ezetimibe (EZE) to ongoing statin therapy in patients with hypercholesterolemia, CHD, or multiple risk factors who required further low-density lipoprotein cholesterol (LDL-C) reduction. The aim of the current analysis was to determine whether EZE had consistent effects on plasma lipids for each of the statins used in this study.
Methods: Patients (n=769) receiving a stable dose of statins for >6 weeks were randomized to placebo (PBO) or EZE 10 mg/d plus their open-label statin regimen for 8 weeks. The primary efficacy variable was % change from baseline to endpoint in LDL-C. Secondary variables included high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG).
Results: Addition of EZE to ongoing simvastatin (Simva), atorvastatin (Atorva), and "Other" statin therapy (lovastatin, pravastatin, fluvastatin, and cerivastatin) resulted in incremental reductions of LDL-C compared with therapy with the corresponding statin alone, as shown in the table below. Significant decreases in TG induced by EZE were also observed within each statin category. The effect of EZE treatment on lipid profiles was consistent across the 3 statin groups (ie, there was no significant treatment-by-statin interaction).

Mean % change (SEM)

Treatment	LDL-C	HDL-C	TG*
Simva+PBO (n=117)	-3.1 (1.3)	2.0 (0.9)	-3.3 (2.5)
Simva+EZE (n=123)	-26.8 (1.3)**	1.3 (0.9)	-13.8 (2.5)**
Atorva+PBO (n=162)	-4.0 (1.1)	0.7 (0.8)	-4.3 (2.5)
Atorva+EZE (n=146)	-25.0 (1.2)**	2.5 (0.8)	-16.2 (2.2)**
Other+PBO (n=111)	-3.8 (1.4)	0.3 (1.0)	-0.2 (3.1)
Other+EZE (n=110)	-23.5 (1.4)**	4.4 (1.0)	-12.1 (2.5)**
Pooled Statin+PBO (n=388)	-3.7 (0.7)	1.0 (0.5)	-2.9 (1.5)
Pooled Statin+EZE (n=375)	-25.1 (0.7)***	2.7 (0.5)**	-14.0 (1.4)**

*Median % changes from baseline; **p<0.05 vs Statin+PBO; ***p<0.001 vs Statin+PBO.

Conclusion: Addition of EZE to ongoing statin therapy led to significant improvements in LDL-C and TG independent of the statin to which EZE was added.

214 Consistency of LDL-C lowering effect across subgroups of ezetimibe co-administered with statins

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Background: Four phase III, multicenter, randomized, double-blind, placebo-controlled studies examined the efficacy and safety of ezetimibe (EZE) administered with atorvastatin (ATOR; 10, 20, 40, 80 mg), lovastatin (LOV; 10, 20, 40 mg), pravastatin (PRAV; 10, 20, 40 mg), or simvastatin (SIM; 10, 20, 40, 80 mg) in patients with primary hypercholesterolemia.
Methods: After dietary stabilization (NCEP Step I or stricter diet), 2-12 wk washout period and 4-wk, single-blind, PBO lead-in period, patients with baseline LDL-C ≥145 mg/dl, ≤250 mg/dl and TG ≤350 mg/dl were randomized to 1 of the following administered daily for 12 weeks: EZE 10 mg; statin 10, 20, 40, or 80 mg; EZE 10 mg + statin 10, 20, 40, or 80 mg; or PBO. Primary efficacy endpoint was % reduction from baseline at endpoint in direct LDL-C for pooled EZE + statin vs statin alone. Secondary efficacy endpoints included % change from baseline at endpoint for HDL-C and TG.
Results: Mean % changes (SEM) from baseline to endpoint in LDL-C for the pooled statin and EZE+statin groups for the subgroups age, gender, diabetes mellitus (DM), and CHD are depicted (see table). EZE + statin provided enhanced reductions in LDL-C vs statin alone across the subgroups examined. A greater increase in HDL-C and greater reductions in TC and TG were also observed with co-administration of EZE+statin compared to statin alone.

Characteristic	N	Statin	N	EZE+Statin	(EZE+Statin)-(Statin) (95%CI)
Age <65 y	669	-31.7 (0.7)	650	-44.5 (0.7)	-12.8 (-14.7, -11.0)
Age ≥65 y	258	-34.6 (1.0)	264	-50.1 (0.9)	-15.5 (-18.0, -12.9)
Male	388	-31.3 (0.8)	395	-44.8 (0.8)	-13.5 (-15.8, -11.2)
Female	539	-33.4 (0.7)	519	-47.1 (0.7)	-13.8 (-15.8, -11.7)
DM Yes	51	-33.3 (2.0)	49	-46.6 (2.4)	-13.2 (-19.4, -7.1)
DM No	876	-32.5 (0.6)	865	-46.1 (0.6)	-13.6 (-15.2, -12.1)
CHD Yes	75	-29.5 (2.0)	75	-47.8 (1.8)	-18.3 (-23.6, -13.0)
CHD No/Unknown	852	-32.8 (0.6)	839	-46.0 (0.6)	-13.2 (-14.8, -11.6)

Conclusions: When co-administered with ATOR, SIM, PRAV, or LOV, EZE provided effects on the lipid profile that were significantly better than statin alone and were generally consistent across the subgroups examined.

215 PPAR gamma agonist L-805645 induces regression of atherosclerotic lesions, decreases inflammation, and increases smooth-muscle cells

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Introduction: Peroxisomal Proliferator-Activated Receptors gamma (PPAR-gamma) are nuclear receptors that modulate several genes that play a central role in lipid metabolism. They are present in macrophages and have been postulated to affect plaque stabilization. Our objective was to investigate the effects of a PPAR-gamma agonist (L-805645) alone or in combination with simvastatin. Effects of plaque size and composition were assessed by serial MRI and by immunohistochemistry.
Method: Experimental atherosclerotic (AT) lesions were induced by balloon denudation and atherogenic diet in rabbits. Following the 9-month induction period, AT lesions were assessed by MRI and the animals matched according to lesion severity and distributed among the following study groups: AT-control (n=5) sacrificed and processed for histopathology. The remaining animals were maintained on atherogenic diet plus the corresponding treatments for additional 6-months: AT-progression (n=5) placebo; simvastatin-group (n=5; 10mg/kg/d); PPAR-gamma agonist (n=6; 10mg/kg/d) and combination simvastatin + PPAR-gamma agonist (n=7). The effect of the treatments was assessed by MRI and histopathology. Vessel wall area (VWA), a surrogate for atherosclerotic burden, was normalized to the baseline (pre-treatment) value allowing each animal to serve as its own control.
Results: All the groups showed similar VWA (8.45±0.65 mm^2) at randomization. AT-progression group showed a significant increased (15%; p<0.01) in VWA while all the treatment-groups showed a significant reduction of the established lesions (-11.7%, -4.5% and -21.8% for simvastatin, PPAR-gamma and the combination respectively; p<0.01). All the treatments reduced the macrophages and increase the smooth muscle cells content of the lesions. In addition, they reduced MMP activity when compared to AT-control animals.
Conclusion: PPAR-gamma agonist (L-805645) reduces the size of established AT lesions. In addition, its effect seems to be additive when combined with simvastatin offering a novel and more effective therapeutic approach in atherosclerosis.

216 The reality of statin use in primary care!

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Management of hyperlipidaemia in patients with ischaemic heart disease is sub-optimal despite the proven benefit of statin therapy. Significant improvement in management has been shown in the EUROASPIRE II study. It is unclear however, whether such changes have also occurred in primary care.
4761 patients were screened from three general practices within the United Kingdom to provide a cohort of 300 patients. 249 (83%) had their cholesterol concentration measured and 141 (47%) were on statin therapy. 129 (43% of total) achieved a target cholesterol of <5 mmol,l of which 85 (64%) were taking statin therapy. Of the remaining 120 patients whose cholesterol exceeded 5 mmol/l, 56 (47%) were taking statin therapy. Thus 60% (85/141)(95% CI 51.2 to 67.4) of those on statin therapy achieved adequate control compared to 40% (44/108)(95% CI 30.9 to 49.8) without statin p<0.008. Those patients with CHD diagnosed on objective evidence were more likely to receive statin therapy than those diagnosed on clinical grounds (55.5% (95% CI 47.5 to 63.2) versus 36.9% (95% CI 29.0 to 45.6); p=0.001. Median doses with 25th and 75th centiles of simvastatin, pravastatin, atorvastatin and cerivastatin were 20mg (10 to 20mg), 20mg (10 to 40mg), 20mg (10 to 40mg), and 150mg (100 to 200mg) respectively.
There is a higher prevalence of cholesterol measurement and statin prescription than in previous series. However, many patients are still not receiving appropriate secondary prevention with statin therapy and many of those that are still fail to achieve target levels. The average doses of statins vary and are lower than the evidence based doses used in large-scale studies, which may help explain the degree of failed treatment.

TISSUE FACTOR: LET'S GO FOR PATHWAYS

217 Inhibition of tissue factor by blockade of NFkB and IKK-2 using gene transfer: NFkB as a therapeutic target for reducing plaque thrombogenicity

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Background: High content of tissue factor (TF), the main initiator of the coagulation cascade in vivo, has been detected in unstable coronary plaques, mainly in macrophages. The TF gene contains non consensus nuclear factor kappa B (NFkB) binding sites. Our aim was to dissect intracellular signalling pathways involved in regulation of TF in human macrophages and endothelial cells, using a highly efficient adenoviral gene delivery system to investigate the role of NFkB and its upstream activators I kappa B-kinase 2 (IKK-2) and IKK-1.
Methods: Elutriation-enriched monocytes were obtained from single donor plateletpheresis residues, and cultured in the presence of macrophage-colony stimulating factor for differentiation to macrophage-like phenotype. Endothelial cells were isolated from human umbilical cords (HUVEC). Cells were left uninfected or infected with adenoviral vectors encoding I kappa B alpha, an inhibitor of NFkB nuclear translocation, or a dominant negative (DN) form of IKK-2 or IKK-1, or without insert as control. A multiplicity of infection of 100:1, at which the efficiency of infection was>95%, was used. After infection, cells were stimulated with Lipopolysaccharide (LPS) or recombinant human soluble CD40 ligand (CD40L), two major stimuli for TF induction. TF antigen was measured by ELISA on cell lysates, and TF activity by a chromogenic assay on whole cells.
Results: NFkB activation is required for TF induction by LPS and CD40L in HUVEC and macrophages, as TF production by both macrophages and endothelial cells was inhibited by 80%±15 and 76%±19 respectively following IkBa overexpression. Overexpression of IKK-2DN in HUVEC significantly reduced TF induced by LPS and CD40L. However, in macrophages, overexpression of IKK-2DN inhibited CD40L-induced TF production (90%±10; p<0.0001), but could only partially inhibit LPS-induced TF expression (36%±14; p<0.004). Similar levels of inhibition of TF activity were observed. The absence of an inhibitory effect of IKK-2DN was paralleled by a lack of inhibition of NFkB nuclear translocation in macrophages, despite efficient overexpression of the transgene, in contrast to HUVEC. Overexpression of IKK-1DN did not affect TF expression.
Conclusion: Blockade of the NFkB pathway in macrophages and endothelial cells inhibits TF induction, suggesting that inhibition of NFkB could be an effective therapeutic target in reducing plaque thrombogenicity. Moreover, our data show selective usage of IKK-2 in NFkB activation and TF expression in human primary macrophages and endothelial cells.

218 Akt negatively regulates tissue factor expression in human endothelial cells

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Activation of the coagulation cascade plays a pivotal role in the pathogenesis of arterial thrombotic disease, in particular acute coronary syndromes. Thrombin induces the conversion of fibrinogen to fibrin, platelet aggregation and tissue factor expression. Thus, thrombin is a key modulator of this positive feedback mechanisms of thrombus formation. However, the signaling pathways responsible for thrombin-induced tissue factor expression in endothelial cells remain unclear. It was the aim of this study to investigate the signaling mechanisms underlying tissue factor induction by thrombin in human aortic endothelial cells (HAECs).
In HAECs, thrombin (4 U/mL) markedly increased tissue factor expression, determined by Western blotting, as well as its cell-surface activity with a maximal induction after 4 to 6 hours of the stimulation. Tissue factor induction by thrombin (6 hours) was concentration-dependent (0.01 to 4 U/mL). Thrombin (4 U/mL) induced the rapid and transient (5 to 10 minutes) increase in Rho A activity, determined by pull-down assay, as well as in p38 MAP kinase and ERK1/2 activities, determined by Western blotting with the phospho-specific antibodies. The Rho-kinase inhibitor, Y-27632 (10 μmol/L) as well as the p38 MAP kinase inhibitor, SB203580 (10 μmol/L) significantly prevented tissue factor induction by thrombin (4 U/mL, 6 hours) ($n = 3$, $P < 0.05$). However, inhibition of MEK/ERK pathway by the MEK1/2 inhibitor, U0126 (10 μmol/L) failed to prevent tissue factor induction by thrombin (4 U/mL, 6 hours). In contrast to Rho A and MAP kinases, thrombin (4 U/mL) induced the rapid and transient (5 to 10 minutes) decrease in Akt phosphorylation and activation level, determined by Western blotting with the phospho-specific antibody. The phosphoinositol 3-kinase inhibitor, wortmannin (100 nmol/L) enhanced thrombin (4 U/mL, 5 minutes)-induced dephosphorylation of Akt. In addition, wortmannin significantly potentiated tissue factor induction by thrombin (4 U/mL, 6 hours) ($n = 3$, $P < 0.05$). Akt dephosphorylation by thrombin (4 U/mL, 5 minutes) was inhibited by Y-27632 but not by SB203580.
In conclusion, Rho-kinase-dependent Akt dephosphorylation and p38 MAP kinase activation are important for thrombin-induced tissue factor expression in human endothelial cells. These findings may provide the molecular insight into the vascular thrombogenicity in acute coronary syndromes.

219 Tissue factor ligand interaction activates stress-activated protein kinase p38 independently of the proteolytic activity of Factor VIIa

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The complex of the transmembrane serine protease receptor Tissue Factor (TF) and its ligand Factor VIIa (FVIIa) modifies intracellular signal transduction pathways. Dependent upon its proteolytic activity FVIIa stimulates protease-activated receptors. In addition, TF ligand interactions induce recruitment of the Actin-binding Protein-280 to the cytoplasmic domain of TF independently of the proteolytic activity of FVIIa and thereby support cell spreading and migration.
Stress-activated kinase-2 p38 enhances intracellular F-actin concentrations by phosphorylation of the F-actin polymerization factor heat shock protein (HSP) 27. Activation of this pathway by oxidants and growth factors results in an increased cell migration
To investigate TF-mediated activation of SAPK-2 p38, smooth muscle cells were incubated with FVIIa and proteolytically inactive FFR-FVIIa. Dose-dependent activation of SAPK-2 p38 kinase activity was found for both ligands to a similar extent. In vitro kinase assays showed an increase in kinase activity by 88±3% after incubation with 500 nM FVIIa and by 75±4% after incubation with 500 nM FFR-FVIIa compared to unstimulated controls. In experiments with the human bladder carcinoma cell line J82, that express high levels of TF, similar results were obtained. The FFR-FVIIa-induced activation of SAPK-2 p38 was specific for TF, because it was abolished by specific inhibitory monoclonal antibodies.
In addition to the interaction of the cytoplasmic domain of TF with the actin-binding protein-280, TF-mediated activation of SAPK-2 p38 may enhance cell motility.

220 Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity

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Background: Several studies suggest a role for circulating tissue factor activity (TF-AcT) in atherothrombotic diseases. We hypothesize the increased BT in T2DM, observed in a previous study was in part mediated by increased circulating TF-AcT. We have extended our study to other certain risk factors such as smoking and hyperlipidemia.

Methods and results: Poorly controlled T2DM patients (n=36), smokers (n=10), untreated hyperlipidemic subjects (n=10) and a group of healthy volunteers (n=15) were studied. T2DM were randomized into a (diet modification plus troglitazone or diet modification plus placebo) for 3 months. Current smokers subjects were advised to smoke two cigarettes. Circulating TF-AcT was determined as FXa generation following the capture of plasma solubilized TF by an immobilized antibody. BT was assessed by Badimon perfusion chamber in T2DM patients. T2DM patients showed significantly higher circulating TF-AcT plasma level, both at baseline and after treatment (370±161 vs 286±163 FXa (pM/min), p=0.0001) than healthy volunteers (195±44, FXa (pM/min), p=0.0001). Patients with improvement in glycemic control showed a significant reduction in circulating TF-AcT (362±135 vs 243±74 FXa (pM/min), p=0.0001) independent of treatment group. However, patients without improvement of glycemic control showed no change in TF-AcT (386.87± 191.04 vs 353.50±221.65, p>0.05). A similar pattern was observed in BT: patients with improvement of glycemic control showed a reduction in thrombus formation (15445±1130 vs 12072±596 $\mu m/mm^2$, p=0.01), while patients without improvement glycemic control achieved no changes in thrombus formation (14236.168± 2310 vs 15362.24±3718.01 $\mu m/mm^2$, p>0.05). The reduction in HbA1c was significantly correlated to the reduction in TF-AcT levels (p=0.014). A positive correlation was also founded between reduction BT and reduction TF-AcT (p=0.007). Smokers increased a 30% TF-Act after two hours to smoke 2 cigarettes (217±72 FXa, pM/min vs 283±106 FXa, pM/min, p=0.003). Hyperlipidemic subjects showed a higher TF-AcT (237±63 FXa, pM/min, p=0.035) than healthy volunteers.

Conclusions: Our observations suggest that the increased incidence of thrombotic complications observed in diabetic, hyperlipidemic and smokers may be related to an increased circulating TF activity. Furthermore, a rationale control of these cardiovascular risk factors could be associated to a reduction of circulating TF-AcT and BT.

221 Tissue factor expression by platelet-monocyte cross talk in stable and unstable angina

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Background: Tissue factor (TF), the major procoagulant in vivo, is usually absent from blood cells. However, monocyte (Mo) TF-expression and platelet activation are both features of unstable angina and may contribute to this prothrombotic state.

Methods: In 60 coronary artery disease patients with stable (SA, n=44) and unstable angina (UA, n=16) MoTF expression and total (CD42) and activated (CD62P) platelet load was determined by flow cytometry on CD14+ cells. MoTF-dependent procoagulant activity (PCA) was measured by chromogenic assay. Prothrombin fragment F1.2 was determined by ELISA and expression of TF mRNA was confirmed by RT-PCR.

Results: MoTF-antigen level (16.4±3.3 MFI), MoTF-PCA (68.5±38.2 U/10e6 PBMC) and activated platelet load on Mo (CD62P:198±130 MFI) were significantly higher in UA compared with SA (14.1±3.1 MFI, p=0.03; 47.9±18.1U/10e6 PBMC, p=0.04; 126±134 MFI, p=0.03). Both, total (r=0.69, p<0.001) and activated (r=0.47; p=0.002) platelet load positively correlated with MoTF Ag-expression, which further correlated with TF-dependent PCA and F1.2 levels. MoTF mRNA was expressed in 26% of SA and in 37.5% of UA.

Conclusion: We show elevated MoTF-antigen expression paralleled by higher MoTF-dependent PCA in UA compared with SA patients correlating with total and activated Mo-platelet load. This suggests increased platelet-leucocyte cross talk contributing to the procoagulant state in acute coronary syndrome.

222 Tissue factor, tissue factor pathway inhibitor and cytoadhesive molecules in patients with acute coronary syndrome

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The tissue factor (TF) plays a crucial role in the initiation of blood coagulation after the plaque rupture in patients with acute coronary syndrome (ACS). The aim of the study was to compare the plasma levels of TF, tissue factor pathway inhibitor (TFPI), soluble P-selectin (sP-s), E-selectin (sE-s) and Intercellular Adhesion Molecule – 1 (sICAM-1) in patients with an acute myocardial infarction (AMI) (n=10), unstable angina pectoris (UAP) (n=23), stable coronary artery disease (SAP) (n=17) and normal control subjects (N) (n=10). In addition, plasma levels of TF, TFPI, sP-s, sE-s and sICAM-1 were measured in the blood drawn from coronary sinus (CS) in subgroup of patients with UAP and SAP and difference between concentrations in the CS and systemic blood was calculated. A significant increase in TFPI plasma levels was detected in patients with AMI (373.3±135.1 ng/mL, p<0.01) and UAP (119.6±86.9 ng/mL, p<0.05) in contrast to the patients with SAP (46.3±37.5 ng/mL) and N (45.1±14.3 ng/mL). The plasma levels of TFPI were significantly increased both in the CS and systemic blood in the patients with the UAP. There was only non-significant trend to higher plasma levels of TF in patients with the AMI and UAP as compared to the patients with SAP and N, the values being, respectively, 129.1±30.2 pg/mL, 130.5±57.8 pg/mL, 120.2±45.1 pg/mL and 124.9±31.8 pg/mL. The difference in plasma levels of sICAM-1 between the blood drawn from CS and systemic circulation was significantly correlated to the corresponding differences in plasma levels of sP-s and sE-s.

In conclusion, TFPI levels are increased both in the systemic blood and in the CS in patients with ACS, thus suggesting that not only local, but also systemic activation of coagulation takes place in patients with ACS.

DEGENERATIVE AORTIC STENOSIS, NEW MECHANISMS

223 Matrix metalloproteinase MMP-2 is upregulated and activated in calcific aortic stenosis

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Background: Fibro-calcification of valve cusps is the main reason for aortic stenosis in the elderly. It is characterized by chronic inflammation and extensive remodeling of the extracellular matrix. The role of matrix metalloproteinase 2 (MMP-2, Gelatinase A), a 72 kDa endopeptidase capable of degrading various components of the extracellular matrix, has not been determined in this disease process.

Methods: Human tricuspid aortic valves with (n=19) and without (n=4) calcific aortic stenosis were obtained at valve replacement or autopsy, respectively. MMP-2 mRNA was determined in tissue homogenate using RT-PCR. Using a monoclonal antibody against MMP-2, immunohistochemistry on cryosections with semiquantitative scoring and Western blotting with densitometric analysis were performed. Gelatinolytic activity of MMP-2 was measured by gelatin zymography and localized by in-situ zymography with or without MMP activation with 1 mmol/L p-aminophenymercuric acetate (APMA).

Results: MMP-2 mRNA expression was detectable in normal and stenotic valves. MMP-2 immunoreactivity was shown in fibroblasts and fibrocytes in all valves. Staining intensity was significantly higher in stenotic valves by semiquantitative scoring (1.3±0.1 vs 0.5±0.0 score units, P<0.001). Western blotting and gelatin zymography demonstrated bands at 72 kDa with higher band intensities in stenotic valves by densitometry. In-situ zymography showed markedly increased gelatinolytic activity in stenotic valves compared to normal valves. On activation with APMA, gelatinolytic activity was significantly increased in normal valves indicating that MMP-2 is present mostly as a latent proenzyme in these valves. In stenotic valves, incubation with APMA did not result in an elevation of MMP-2 activity indicating that MMP-2 is present already in an activated form in these valves.

Conclusion: MMP-2 is constituously present in human aortic valves and upregulated in calcific aortic stenosis. In normal valves, MMP-2 is present mainly as latent proenzyme with low gelatinolytic activity. In stenotic valves, MMP-2 is activated. These results may indicate a pathogenetic role of MMP-2 in the tissue remodeling in calcific aortic stenosis.

224 The role of matrix metalloproteinases in aortic valve diseases

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Background: Human cardiac valve diseases are characterised by pathological remodelling of valvular tissue but the cellular and molecular effectors involved in these processes are not well known. Here, we investigate the role of matrix metalloproteinases (MMPs) MMP-3 and MMP-7 in human aortic valve diseases.
Methods: Pathological valves were collected during surgery, and the controls, non-cryopreserved homografts, were obtained from a human tissue bank. Valves were classified according to their pathology and divided into 3 groups: aortic controls (n=10), aortic stenosis (AS) (n=51), aortic regurgitation (AR) (n=24). Valves were studied histologically at the cellular and extracellular matrix levels. The biochemical analyses (casein zymography, reverse zymography and Western blot) were performed on valve extracts and valve conditioned media (valvular tissue incubated in basal culture medium during 24 hours).
Results: Histological study showed fibrotic, inflammatory and calcified lesions in AS, and degenerative lesions characterised by disorganization of collagen bundles and elastic fibers in AR. Zymography of extracts showed that the MMP-3 activity was significantly increased in AS compared to controls ($p<0.001$) and AR ($p<0.05$) (AS: 8960 ± 1140; AR: 5570 ± 1620; controls: 770 ± 436 densitometric units/μg of proteins). It was also increased in AR compared with aortic controls (NS). In extracts, the MMP-7 activity was significantly increased in AS compared with aortic controls ($p<0.05$) (AS: 5710 ± 1200; AR: 2750 ± 1540; controls: 18 ± 18 densitometric units/μg of proteins). MMP-3 and MMP-7 were absent from conditioned media; this was confirmed by Western blot. Thus, MMP-3 and MMP-7 are stored in the extracellular matrix and do not diffuse into the culture medium.
Conclusion: This study demonstrates the involvement of the MMP system in the extracellular matrix remodelling of both dystrophic and degenerative aortic valve diseases. In addition, these results provide clear further proof of the inflammatory state of the pathological valves, especially in AS.

225 Smoking cessation: transdermal nicotine system (TNS) use among medical staff

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Introduction: Majority of doctors and nurses believe that their duty is to help patients to give up smoking. The aim of the study was to assess smoking habit and the efficacy of TNS (which delivered nicotine at 0.7 mg/cm^2/24 h) among medical staff-smokers in Clinical Hospital Split.
Methods: The sample consisted of 311 persons: 207 (66.6%) females, 104 (33.4%) males, 119 (38.3%) doctors, 192 (61.7%) nurses. There were 112 (36%) smokers: 36.7% (76/207) females, 36.5% (38/104) males, 36.9% (44/119) doctors, 36.5% (70/192) nurses.
In a randomised double-blind study during 3 weeks included were 112 smokers subdivided in 2 groups: TNS and placebo. Abstinence was evaluated with questionnaires and measuring CO in expired air.
Results: The abstinence rates after 3-week period were 39.3% in the nicotine group and 19.6% in the placebo group. The difference was significant ($p<0.05$). Five years later in the observed population there were 101 (32.5%) smokers: 37.7% (78/207) females, 17.3% (18/104) males, 20.2% (24/119) doctors, 38% (73/192) nurses. There was no difference between the former TNS and placebo group.
Conclusions: This study has shown that short TNS treatment is effective in smoking cessation. Five years later in the observed population there were less smokers (-3.5%, n.s.), especially among doctors (-16.7%,$p<0.01$) and males (-19.2%,$p<0.01$). Further intervention in this field, like drug application is necessary, particularly among nursing staff.

226 Increased thermal heterogeneity in degenerative aortic valve stenoses: first human application of aortic valve thermography catheter

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Background: Recent studies suggest that valvular degeneration in aortic valve stenosis (AVS) could be caused by inflammatory processes. Inflammation leads to heat release locally in atherosclerotic plaques. Thus, the present study was designed to investigate whether thermal heterogeneity is present in patients (pts) with and (AVS) by the first human application of an aortic valve thermography catheter.
Methods: The study population consisted of 10 pts with AVS undergoing diagnostic catheterization (mean age: 74.2 ± 8.1 yrs) and 8 pts without AVS (mean age 70.1 ± 9.3 yrs) undergoing diagnostic catheterization for the evaluation of chest pain. In pts with AVS an echocardiography was performed before the catheterization, and mean and maximal pressure gradient was estimated. Temperature measurements were performed by an aortic valve thermography catheter, previously validated. This thermography catheter is 8F in diameter and its proximal part is attached to a connector with a hemostatic valve and to a connector for the thermistor lead-wires. A steering arm passes through the hemostatic valve, and through the lumen of the catheter and is attached to the tip of the catheter. The distal 20 cm of the shaft of the catheter consist of a soft non-thrombotic material and enable this distal part to be curved to 90°. The thermistor lead-wires end to the connector and pass through the lumen of the catheter. The thermistor probe is positioned at the tip of the catheter. Manipulation of the steering arm at the proximal end enables the distal end of the catheter to be altered by remote control so that the thermistor is in contact with the aortic valve or aortic wall. Temperature was measured at different sites of the aortic valve and also on the wall of the ascending aorta. The maximum difference between the temperature of aortic valve and aortic wall was designated as temperature difference (TD).
Results: The procedure of temperature measurement of the aortic valve and the aortic wall in the ascending aorta was successful, without any complications in the whole study group. TD was increased in pts with AVS compared to the subjects without AVS (0.54 ± 0.5 vs 0.05 ± 0.01°C, $p < 0.01$). Moreover, in pts with AVS the mean and maximal pressure gradient was not correlated with TD.
Conclusions: The first human application of an aortic valve thermography catheter was successful and uncomplicated. Thermal heterogeneity is frequently found in human aortic valves in pts with AVS. Further research is warranted in order to evaluate this phenomenon during the progression of aortic valve stenosis.

227 Do really statins reduce the progression of aortic stenosis? A need for a prospective randomized trial

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Background: It has been recently suggested in a retrospective study of 57 statin-treated patients with mild to moderate aortic stenosis (AS) that statins could slow the progression of AS (Circulation 2001; 104:2205-9).
Methods: From our echocardiographic database (1988-2001) we obtained 95 statin-treated patients with mild to moderate AS (initial peak aortic velocity 2-3.9 m/s) and with at least two examinations >6 months one apart of the other (61 males, 34 females, mean age 67.6 ± 8.6 years, mean follow up 54 ± 36 months; initial aortic valve area 1.28 ± 0.26 cm^2). As control group we randomly selected, from the remaining 759 patients with an initially similar degree of AS and with at least two examinations, 95 sex-age matched patients who did not receive treatment with a statin (61 males, 34 females, mean age 67.5 ± 8.7 years, mean follow up 51 ± 34 months; initial aortic valve area 1.28 ± 0.25 cm^2).
Results: The rate of increase of peak aortic velocity was 0.15 ± 0.26 m/s/year in the statin group and 0.15 ± 0.20 m/s/year in the control group (p=ns). The rate of decrease of aortic valve area was – 0.074 ± 0.095 cm^2/year in the statin group and 0.069 ± 0.074 cm^2/year in the control group (p=ns). The mean value of aortic valve area at the end of the study was 1.01 ± 0.31 cm^2 in the statin group and 1.04 ± 0.30 cm^2 in the controls (p=ns). A pattern of rapid progression of AS (increase of peak aortic velocity > 0.3 m/s/year) was observed in 20/95 (21%) of statin-treated patients and in 15/95 (16%) patients who did not receive statins (p=ns). A major clinical end point (death or aortic valve replacement) was found in 21/95 statin-treated patients (22%) and in 13/95 (14%) not treated patients (p=ns).
Conclusion: Despite the theoretical potential benefits of statins on aortic valve lesion, our study does not confirm the first results about their slowing effect on the progression of AS. A prospective randomized controlled trial is then necessary before to extend the indications of statins to patients with AS.

FACILITATED AND RESCUE PERCUTANEOUS CORONARY INTERVENTION IN ACUTE MYOCARDIAL INFARCTION

255 Effects of facilitated percutaneous coronary intervention on myocardial perfusion and clinical outcome in patients treated with tenecteplase and eptifibatide for acute myocardial infarction

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Background: Recent data suggest that patients with ST elevation myocardial infarction (AMI) arriving in the cath-lab already with TIMI 3 flow of the infarct-related artery have a higher success rates of PCI and an improved clinical outcome. These findings have renewed the interest in facilitated percutaneous intervention (PCI) following medical reperfusion therapy.
Methods: Patients with AMI < 6 hrs were treated with different combinations of reduced-dose tenecteplase and double-bolus regimens eptifibatide in the INTEGRITI study. After patients underwent protocol-mandated angiography at 60 min, facilitated PCI was performed at the discretion of the investigator. We report the results of 97 patients with PCI at 60-90 min after start of thrombolysis.
Results: TIMI 2 or 3 flow before PCI was observed in 21% and 65% of the patients, respectively. Complete (> 70%) ST resolution was seen in 52% before PCI. The intervention was successful in all patients. A stent was implanted in 84/97 of the patients. After PCI all patients had a patent infarct-related artery with TIMI 2 and 3 flow in 9% and 91% of patients, respectively. This resulted in a rate of 81% complete ST resolution 90 min after PCI. Until day 30 we observed 5 deaths, no reinfarction, 1 re-PCI and 3 CABG. TIMI major bleeding occurred in 4 patients.
Conclusion: Facilitated PCI after combination therapy with eptifibatide and reduced-dose tenecteplase is associated with a high rate of epicardial coronary artery patency and myocardial tissue reperfusion and a low rate of reinfarctions and re-interventions. The impact of this combined medical and interventional approach on clinical outcome in patients with AMI will be evaluated in a phase III study (ADVANCE-MI).

256 Microvascular no-reflow phenomenon and myocardial injury after facilitated angioplasty in patients with acute myocardial infarction

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Drug-facilitation of coronary angioplasty in acute myocardial infarction (AMI) is expected to reduce microvascular no-reflow and thus myocardial injury.
We compared invasively-determined parameters of coronary flow (TIMI scale and corrected TIMI Frame Count, CTFC [frame]) and perfusion (TIMI Myocardial Perfusion Grade, TMPG) with biochemical injury (area under the curve of CK-MB release within the first 24 hours, CK-MB24 [U/l x h]) and echocardiographic LV function (ejection fraction, EF [%] 48 hours after the procedure) in 126 consecutive patients (pts) with AMI (mean age 57.1±10.1 years). All pts (52 pts with anterior, 18 pts with lateral and 56 pts with inferior AMI) received half-dose of actilyse plus abciximab before coronary angiography. PCI was subsequently performed in 111 pts.
TIMI-3 was achieved in 73 [65,8%] before and 104 [93,7%] pts after PCI, TIMI-2 in 17 before and 7 pts after PCI, and TIMI-0/1 in 21 befor and 0 pts after PCI. TMPG-3 was achieved in 63 [56,8%] before and 55 [49,9%] pts after PCI, TMPG-2 in 22 before and 31 pts after PCI and TMPG-0/1 in 26 before and 25 pts after PCI. CTFC was 26,1±15,3 before and 19,2±11,3 after PCI ($p<0.05$). Mean EF in TMPG-3 vs. TMPG<3 pts was 62.8±9.4 vs 56.3±7.4 ($p<0.001$) whereas CK-MB24 was 2316±1205 vs. 2895±1773 ($p=0.015$). Mean EF in TIMI-3 vs. TIMI<3 was 60.9±8.1 vs. 56.9±10.3 ($p=0.03$). The table shows the values of mean EF and CK-MB24 in relation to TIMI before and TMPG after PCI.

EF, CK-MB24 in relation to TIMI and TMPG

	TIMI-3 before PCI	TIMI<3before PCI	TIMI<3before PCI	TIMI<3before PCI
	EF [%]	EF [%]	CK-MB24 [U/l x h]	CK-MB24 [U/l x h]
TMPG-3 after PCI	62.5±7.5 (n=48)	65.1±6.4 (n=7)	2206.4±1010.1	3139.8±1632.4
TMPG<3 after PCI	57.8±8.4 (n=25)	55.6±10.2 (n=31)	2851.4±1650.3	2984.9±1551.3

For abbreviations see text of abstract

Conclusion: Achievement of high TMPG with facilitated PCI in AMI is associated with limited myocardial injury independent of initial TIMI flow.

257 Prehospital thrombolytic/abciximab therapy in comparison to PTCA/stent after combined prehospital thrombolysis in acute myocardial infarction

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Background: Prognosis in acute myocardial infarction (AMI) is mainly determined by early reperfusion and the restoration of a normal blood flow in the infarct related artery. However, reperfusion therapy for AMI with thrombolysis has been shown to achieve a 50% TIMI-3-flow only. Early trials combining thrombolysis and PTCA have failed to show a mortality benefit mainly due to encountered bleeding complications. Since the reduced fibrinolytic therapy in combination with a platelet glycoprotein IIb/IIIa inhibitor (COMBO) has recently shown to reduce the rate of AMI related complications, "facilitated" PTCA with stent implantation needs new evaluation.
Methods: Since 12/2000 110 patients with an AMI were randomized in Leipzig, Germany within 6 hours after symptom onset to either a prehospital COMBO (half dose Reteplase + abciximab) with in-hospital conservative therapy (n=54) and elective cardiac catheterization or a prehospital initiated COMBO therapy with immediate in-hospital "facilitated" PTCA plus stent implantation (n=56).
Results: Three patients (3%) had to be excluded due to ECG-misinterpretation. Mean time from symptom onset to medical aid was 112±80 min in COMBO only in comparison to 105±40 min in the COMBO+stent group (p=n.s.). In the COMBO only group 12 patients (22%) had to undergo rescue-PTCA due to failed thrombolysis. In the COMBO+stent group mean TIMI-3-flow before intervention was 55% and after 94%, respectively. Mean CK expressed as area under the curve was 959±900 in the COMBO only versus 610±490 µmolh/l in the COMBO+stent group (p=0.059). Four patients in the COMBO+stent had a major bleeding and 2 patients in the COMBO only group (p=n.s.). Mortality and target vessel revascularization procedures were similar in both groups.
Conclusion: The prehospital combined thrombolytic therapy with abciximab is feasible and initial results suggest that a "facilitated" PTCA results in smaller myocardial infarctions as measured by CK-release without excess in encountered complications.

258 Abciximab initiated before transportation of patients with myocardial infarction for treatment by primary angioplasty improves clinical outcome

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Background: Abciximab given before primary angioplasty with stent placement for myocardial infarction (MI) improves clinical outcome. This study was done to compare the outcomes after abciximab initiated before transport for primary percutaneous intervention with abciximab started after arrival in the catheterization laboratory.
Methods: 6 month clinical outcome was evaluated of all patients (pts) with extensive anterior MI, referred for direct angioplasty (n=370), in whom abciximab was initiated either on arrival at our catheterization laboratory (Group A) or at referring hospitals before transport to our tertiary care center (Group B). All pts were treated with an abciximab bolus of 0.25 mg/kg I.V. followed by infusion of 0.125 µg/kg/min I.V. for 12 hrs.
Results: From May 1999 to September 2001, 270 pts (age 61±9 yr; 76% Male) were transported without abciximab prior to transport (group A) and 100 pts (age 61±10 yr; 68% Male) in whom abciximab was started in the referring hospital before ambulance transport. The ambulance transport time in both groups was comparable (45±15 min, range 15-60 min). Established coronary artery disease was more frequent in group B (n=38; 38%) compared to group A (n=70; 26%; p=0.04), but other baseline characteristics were similar. Major vascular complications occurred in 7% (n=19) of the pts in group A vs. 8% (n=8) of the pts in group B (NS). In both groups the rate of revascularization procedures within 6 months were similar (n=38; 14% vs. n=15; 15%, NS). In group A, acute coronary syndromes within the first 6 months were more frequent compared to group B (n=48; 18% vs. n=9; 9%; p=0.04). There was no difference in the mortality rate between the groups (n=24; 9% vs. n=8; 8%; NS). The combined end point of non-fatal cardiac events (acute coronary syndromes + any revascularization) was more frequent in group A (n=96; 36%) in comparison to group B (n=24; 24%; p=0.04). Survival without major adverse cardiac events (non-fatal and fatal cardiac complications) was more likely in group B (75%) than in group A (64%; p=0.04).
Conclusion: Abciximab initiated before transportation for primary angioplasty improves 6 month clinical outcome in pts with acute anterior wall myocardial infarction. Although no mortality difference could be demonstrated in this analysis, it still provides an argument for starting abciximab as early as possible and if applicable before transportation to a tertiary care center for percutaneous intervention in pts with extensive MI.

259 Facilitated PTCA in acute myocardial infarction. A meta-analysis of available studies

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Background: The rapid restoration of normal blood flow in the infarct-related artery is the main objective in the treatment of patients with Acute Myocardial Infarction (MI). This goal is usually accomplished with either fibrinolytics or with primary angioplasty (PTCA). However, both methods have several drawbacks. Recently, the term "facilitated PTCA" has emerged to describe a number of different strategies that aim to use pharmacologic agents (fibrinolytics, GP IIb/IIIa inhibitors) to improve the outcome of early PTCA in acute MI. However, to date there are only small, preliminary studies assessing different combination of pharmacologic strategies that compared facilitated PTCA with standard treatment and results are variable. Thus, the present investigation refines these values by means of a formal meta-analysis.
Methods: Six studies were considered suitable for analysis. Odd Ratios (OR) were calculated for 30-days follow-up. Primary end points were a composite of death and non-fatal MI as well as major bleedings, as considered in every single study. Secondary end points were a composite of death, reinfarction and target vessel revascularisation, according to single study definition, and individual cardiac events as well.
Results: A total of 2332 patients were included. At 30 days, the OR for death and non-fatal MI was 0,70 (95% Confidence Interval [IC], 0,50-0,98, p=0,04) in favor of facilitated PTCA. On the other hand, major bleedings were more frequent in patients treated with facilitated PTCA (OR 1,16, 95% CI, 0,84-1,60, p=NS). According to secondary end points, there was a trend toward less mortality (OR 0,70, 95% CI, 0,45-1,10, p=NS) and less non-fatal MI (OR 0,70, 95% CI, 0,43-1,13, p=NS) in favor of facilitated PTCA. Revascularisations were significantly less frequent (OR 0,50, 95% CI, 0,33 -0,74, P=0,0006) in patients treated with facilitated PTCA compared to standard therapy.
Conclusions: According to 30-days clinical outcomes, the present meta-analysis demonstrates that facilitated PTCA has a superior clinical efficacy compared to standard treatment in acute MI. However, our conclusions suffer strong limitations due to consistent differences in pharmacologic treatments applied and the underpowered sample size of each trial. Therefore, randomized, adequately sized trials, to specifically test the safety and efficacy of facilitated PTCA and the correct target population, should be performed. In fact, the logistical and economical rebounds of a widespread application of facilitated PTCA are enormous.

260 Rescue angioplasty for failed fibrinolysis: can we identify those patients who do not benefit?

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Introduction: There is no consensus regarding the management of patients with acute ST segment elevation myocardial infarction who have early evidence of failed fibrinolysis (FF). Clinical studies of rescue angioplasty (RA) to date suggest low mortality with a successful procedure, but high mortality with a failed procedure. Whether this reflects a high-risk group or harm in some patients is unclear.
Methods: Clinical variables from a large cohort of patients undergoing angiography after FF were analysed to determine the characteristics of patients who did not benefit from RA.
Results: 324 patients (219M, 95F, mean age 62.6 yr) underwent emergency coronary angiography for FF. Mean treatment times were: (a) onset of pain to lysis 206 mins; lysis to cath lab 196 mins; onset of pain to cath lab 405 mins. 30-day mortality was 9.9% (n=32). 84 patients had TIMI 3 flow in the infarct-related vessel (IRV). 240 patients had < TIMI 3 flow. RA was attempted in 220 patients with < TIMI 3 flow ("RA cohort") and not in the remaining 20, either because angiography produced TIMI 3 flow (n=6) or the anatomy was unsuitable (n=14). Of the RA cohort, 178 (81%) had a successful RA procedure (no death/emergency CABG/TIMI 3 in IRV) [Group A]. 41 underwent RA but final flow was < TIMI 3 [Group B]. 30-day mortality for A and B was 8.5% (n=15) and 29.3% (n=12). 30-day mortality in the RA cohort was 12.3% (n=27). In the 84 with initial TIMI 3 flow, 30-day mortality was 4.8% (n=4). Group B patients were significantly older than Group A patients (mean 66.1 vs. 61.2, p=0.004), had longer pain - lysis times (mean 251 mins vs 203 mins, p=0.06), were more likely to be diabetic (22% vs. 9%, p=0.028) and were less likely to be current smokers (22% vs. 30%, p=0.048). Lysis - lab times were similar in Group A and Group B (210 and 221 mins). Pain - lab times were longer in Group B (470 vs. 419 mins, p=0.05) reflecting the longer pain - lysis time.
Conclusion: Failure to obtain adequate antegrade flow during attempted rescue angioplasty for failed fibrinolysis is more likely in long pain to lysis times, increasing age, diabetics and non-smokers. Clinical variables may be helpful in selecting patients for a strategy of rescue angioplasty after failed fibrinolysis.

THE SPECTRUM OF INFECTIVE ENDOCARDITIS

274 Short-term prognosis of infective endocarditis in a one-year French prospective cohort

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Objective: To study the short-term prognosis of infective endocarditis (IE) in a large unselected cohort.
Methods: We collected data on all patients hospitalized for IE during year 1999 in several French regions. For each patient, a case report form was filled in by the clinician (clinical and echocardiographic data) and by the microbiologist (microbiological data). Only definite IE according to the Duke criteria were included (559 cases). Tested variables were: age, gender, comorbidities, cardiac history, at-risk procedures and situations, severity of IE (maximal NYHA class, left ventricular ejection fraction, blood creatinine level > 180 µmol/l, Glasgow score, septic shock), vascular phenomena (embolisms, mycotic aneurysm...), immunologic phenomena (glomerulonephritis, Osler's nodes, rheumatoid factor...), signs of infection (C-reactive protein > 120 mg/l, white blood cells > 10,000...), echocardiography findings (location, abscess, prosthesis dehiscence...), and microorganism.
Results: Mean hospital length of stay was 49.7 ± 43.5 days (range: 1-433). In-hospital lethality rate was 17%. In multivariate analysis, it was significantly influenced by: diabetes mellitus: odds ratio: 7.5 [95% confidence interval: 2.5-22.2]; history of immunodepression: 3.5 [1.6-7.6]; type I septic shock: 4.2 [2.1-8.7]; Glasgow score < 8: 2.4 [1.2-4.7]; history of congestive heart failure: 2.5 [1.3-4.7]; NYHA class III or IV: 2.4 [1.4-4]; C-reactive protein > 120 mg/l: 2.8 [1.6-5.1]; mitral location: 1.8 [1.1-3]; intracranial hemorrhage: 8.8 [2.3-34.5]. During the initial hospital stay, 47% of the patients were operated on. The surgery rate was significantly influenced by: age: (ref: <60 years) 60-70 years: 0.48 [0.29-0.80]; 70-80 years: 0.36 [0.22-0.59]; >80 years: 0.03 [0.01-0.14]; history of dyslipidemia: 2.1 [1.1-3.8]; history of native valve disease: 1.5 [1-2.3]; NYHA class III or IV: 2.9 [1.8-4.5]; aortic location: 3.3 [2.1-5.2]; mitral location: 2.3 [1.5-3.6]; abscess at echocardiography: 2.9 [1.6-5.1]; white blood cells > 10,000: 0.6 [0.4-0.9]; embolism other than cerebral, coronary, lower limbs, pulmonary: 2.0 [1.1-3.5]; intracranial hemorrhage: 0.2 [0-0.8].
Conclusion: Our analysis confirms several variables as factors that influence the lethality rate (e.g., intracranial hemorrhage, heart failure...) or the surgery rate (age, embolisms...). But our multivariate analysis shows interesting findings: when other prognostic variables like comorbidities are taken into account, the outcome of IE may be similar whatever the responsible microorganism.

275 Long-term results of homograft aortic valve replacement for endocarditis

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Background: Homografts were considered to be the ideal aortic valve substitute. Especially in active endocarditis their pre-treatment with antibiotic solutions and their ability to mold well into the fragile infected aortic annulus was thought to be of advantage. However there are sparse data on the long-term course of this valve type especially in regard to recurrent endocarditis.
Methods: Between 1990 and 1997, a total of 90 cryopreserved aortic homografts were implanted (mean patient age 44±14 years). N=26 had active infective endocarditis (group 1), out of these n=8 prosthetic valves were affected. N=64 had non-endocarditic valve lesions (group 2). In a prospective study patients were examined clinically and echocardiographically at yearly intervals (mean 5.3±3.6 years). Follow-up was complete in 85 cases (94%).
Results: 30-day mortality was 4% in group 1 and 5% in group 2. There were eight late deaths in group 1 and five in group 2. Eight patients in group 1 underwent reoperation during follow-up: indications were recurrent endocarditis in three patients, aortic insufficiency in two patients, aortic stenosis in two patients and ventricular septal defect in one case. In group 2 sixteen reoperations were caused by aortic insufficiency(n=7), homograft valve endocarditis(n=5), primary malfunction(n=2), homograft stenosis(n=1) and combined lesions(n=1). At five years actuarial freedom from homograft valve endocarditis was 75% in group 1 compared to 94% in group 2 (p<0.05).
Conclusions: Valve replacement in the presence of native and prosthetic endocarditis remains a surgical challenge. The role of homografts was questionable since in our study a high rate of recurrent graft endocarditis and structural valve deterioration led to subsequent reoperations in patients with endocarditis as well as in cases with non-endocarditic valve lesions.

276 Systemic arterial embolism in patients with infective endocarditis. A reappraisal in a cohort over two decades

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Emboli is one of the complications that may occur in patients with infective endocarditis, associated with significant morbidity and mortality. Surgical treatment may be indicated in some patients. There are few recent reports of embolism in large series of patients with infective endocarditis. We evaluated clinical characteristics of systemic arterial embolism in a large cohort of patients over the last two decades.

Methods - we studied systemic arterial embolism in 824 episodes of infective endocarditis, from October 1978 to December 2001. The ages of the patients ranged from 0.1 to 84 (36.6 ± 17.7) years; 533 (65%) occurred in men and 291 (35%)in women. The infecting microorganisms were the streptococci in 329 (40%) episodes, enterococci in 57 (7%), S. aureus in 144 (17%), S. epidermidis in 65 (8%) and others in 132 (16%). In 97 (12%) the infecting microorganism was not identified. Surgical treatment was performed in 311 (38%) patients. Prosthetic valve endocarditis occurred in 279 (34%) episodes. Overall 214 (26%) patients died.

Results - 144 (17%)emboli were observed, 79 (55%)of them to the central nervous system and 65 (45%) to other arteries. Forty-one (28%) complications occurred before hospital admission, 20 (14%) on the day of admission, 31 (22%) before day 7 of hospitalization, 23 (16%) between days 7 and 15, 9 (6%) between days 16 and 21, 8 (6%) between days 22 and 28, 12 (8%) after 28 days. Fifty-five (38%) patients died.

The frequency of emboli was higher in prosthetic valve endocarditis (62/144, 43%) relative to native valve endocarditis (82/144, 57%)(p=0.01), in patients operated upon (62/144, 43%) relative to those submitted to medical treatment (82/144, 57%)(p=0,04), and in patients who died (55/144, 38%)relative to the survivors (89/144, 62%)(p=0.0002), and was not associated with age, sex and distribution of the infecting microorganisms.

In conclusion, the incidence of embolism in this series was 17% and decreases over time; a significant proportion of embolism occurred before hospital admission or on the day of admission. Prosthetic valve endocarditis was associated with a higher rate of embolism; mortality was also higher in patients with embolism.

277 Aorto-cavitary fistulization in complicated endocarditis. Clinical and echocardiographic features and prognostic factors of mortality

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Background: Spread of infection in infective endocarditis (IE) from valvular structures to the surrounding perivalvular tissue results in periannular complications, which may rupture internally with the subsequent development of aorto-cavitary fistulas.

Objective: To investigate the clinical, echocardiographic and microbiologic features and prognostic factors of in-hospital mortality in patients with IE and aorto-cavitary fistulization.

Methods: Retrospective and multicentre cohort study at 11 Spanish Hospitals. Patients with IE and aorto-cavitary fistula diagnosed by TTE or TEE were included. A descriptive analysis of clinical, echocardiographic, microbiologic and evolutive variables and an univariate analysis of prognostic factors of in-hospital mortality were performed.

Results: Fifty-six patients were identified since 1992, representing 2.2% of all cases of IE, 39 (69%) were male, mean age 50.3 years (range 18-77). Prosthetic valve endocarditis was present in 24 (42%) cases and native valve IE in 32 (57%). All patients had aortic valve involvement and 18 (32%) had multivalvular infection. Embolic phenomena and complete AV block previous to surgery were detected in 12 (21%) and 7(12%) cases. Congestive heart failure (CHF) was present in 34 (60%). Streptococci were detected in 18 (32%) cases, S. aureus in 12 (21%), S. epidermidis in 12, and other microorganisms in 9 (16%). No pathogen was isolated in 4 cases. Echocardiography detected grade III or IV valvular regurgitation (VR), vegetations >10 mm and periannular abscesses in 26 (46%), 25 (44%) and 44 (78%) cases. Fistula developed from the right, left and non-coronary sinuses of Valsalva in 20, 17 and 19 cases. Fistulas communicated with the right atrium in 15 (26%) cases, right ventricle in 14 (25%), left atrium in 12 (21%) and left ventricle in 14 (25)% patients. There were 7 multiple fistulas and a ventricular septal rupture was also present in 9 (16%) cases. Surgery was performed in 52 (93%) patients using different techniques (closure and valve replacement). Overall mortality was 39%. Mortality for native and prosthetic valve endocarditis was 34% and 45% respectively (p=NS). There was no relationship between the involved sinus of Valsalva and higher mortality. Mortality in patients with CHF and with severe VR was 47% and 38%, respectively.

Conclusions: Aorto-cavitary fistulization in complicated IE with periannular extension occurs in patients with high grade of local destruction. It is associated with severe complications, increased requirement of surgery and high in-hospital mortality.

278 Long-term prognosis of patients with prosthetic versus native valve infectious endocarditis after initial successful therapy

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It is well known that prosthetic valve endocarditis (PE) has a worse in-hospital prognosis than native valve endocarditis (NE). Our aim was to compare the long-term prognosis of patients with PE vs NE.

The study group is comprised by 151 patients with endocarditis. Of them, 46 (30%) had PE and 105 (70%) NE. The mean follow-up after discharge was 3.1 years. Patients with PE were older (60+11 vs 48+20 yr, p<0.01), and had a higher frequency of female gender (50% vs 27%, p<0.01), heart failure at admission (59% vs 33%, p<0.01) and S. epidermidis as etiological germen (24% vs 8%, p<0.01). Patients with NE were drug abusers more frequently (37% vs 4%, p<0.01) and had S. aureus as etiological germen more frequently (36% vs 20%, p=0.04). During hospitalization, no significant differences were found between PE vs EN in mortality (22% vs 14%, p=NS), but surgery was required more frequently in PE (65% vs 38%, p<0.01). Of interest, mortality during follow-up was higher in PE (see figure and table).

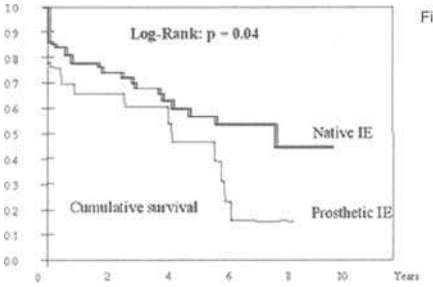

Fig. 1: Long-term outcome

Prosthetic vs Native valve IE	Prosthetic	Native
1 year	30%	22%
5 year	53%	40%
9 year	84%	55%

Thus, the higher mortality rate of PE is specially observed during follow-up rather than during hospitalization. This implies that a close follow-up of patients with PE is needed after discharge.

279 Incidence and characteristics of infective endocarditis in pacemaker recipients in France

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Pacemaker (PM) infective endocarditis (IE) is a serious complication of permanent transvenous pacing. The aim of our study was to evaluate the incidence of definite PM-related IE and to compare characteristics of IE in pts with or without PM leads involvement. We therefore reviewed all the charts of PM recipients included in a cross-sectional prospective population-based survey on IE that was conducted in 7 French regions (17 million inhabitants) in 1999. Based on the results of echocardiographic and/or macroscopic and bacteriological data from extracted material, IE was classified as PM-related or valvular-related.
Among 559 pts included in the database, 45 (8%) had a permanent PM. Incidence of endocarditis was estimated at 460 cases/million of PM recipients/year. Among those 45 pts, 32 had PM-related IE (gr 1; 17 PM alone, 9 PM + tricuspid, 6 PM + left heart valves) and 13 had only valvular-related IE (gr 2; 5 mitral, 4 aortic, 2 both mitral and aortic, 1 tricuspid alone, 1 unknown). Mean age was 69±12 yrs, similar in both groups. A valvular prostheses was present in 3 gr1 and 8 gr2 pts. More than one previous surgical procedure on PM was recorded in 21/30 (70%) vs 3/13 (23%) pts (p=0.01). A procedure-related complication occurred in 8/30 vs 1/13 pts (p=0.23). For those 24 pts, mean delay between last procedure and diagnosis of IE was shorter in gr 1 than in gr 2 (2.0 ± 2.0 vs 5.0 ± 3.3 yrs, p<0.04). Staphylococcus aureus was the causative microorganism of IE in 25 (78%) gr1 pts and in 5 (38%) gr2 pts (p=0.02). A vegetation was seen at echo in 27 gr1 pts vs 9 gr2 pts (ns). An embolic event was noted in 12 gr1 (10 pulmonary, 3 others) vs 3 gr2 (3 others) pts (ns). PM was removed in 26 gr1 (81%) pts (19 surgically, 6 percutaneously, 1 unprecised) vs 2 gr2 (15%) pts (1 surgically, 1 percutaneously) (p=0.0001). A new PM was implanted in 17 gr1 (12 with epicardial electrodes) vs 2 gr2 pts (1 epicardial). In-hospital death occurred in 2 gr1 (6%) pts vs 3 gr2 (23%) pts (p=0.13).
Annual incidence of PM-related IE is intermediate between the incidence of IE in the general population and on prosthetic valves. One third of IE in PM recipients was considered as unrelated to PM and may not require PM removal. Multiple procedures on PM increases the risk of PM-related IE. Surgical or percutaneous PM removal remain the main procedure for treatment of PM-related IE.

SUCCESS OF CORONARY STENTING: IS IMAGING NEEDED?

280 Scintigraphic changes in myocardial perfusion after coronary stent implantation

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Early ischaemic defects at Myocardial Perfusion Scintigraphy (MPS) occur in 30 to 50% of patients submitted to balloon angioplasty. A high proportion of these defects are not observed in scintigraphic studies performed after 3 months. There is very little information regarding the incidence and natural history of early ischaemic defects after coronary stent implantation.
Methods: 35 patients with reversible scintilographic perfusion abnormalities (demonstrated by either exercise or pharmacologically by dipyridamole or adenosine) were submitted to elective successful coronary angioplasty and stenting. Patients underwent MPS within 48 hours after coronary stenting and, again, after 3 months.
Results: In 9 patients (26%), MPS was normal early after stenting. Early mild to moderate reversible myocardial defects were detected in 26 patients (74%), of whom MPS findings were similar to pre-procedure in 8 (23%) and improved in 18 (51%). Before the first 3 months post-procedure 6 patients (17%) underwent new angioplastic studies preceded by MPS due to new onset angina. Of these 6 patients, 5 presented with in-stent restenosis and 1 with a new obstructive lesion in a vessel not treated in the index procedure. In 5 of these patients, the pre angio MPS revealed worsening of myocardial ischaemia. At 3 months, when compared to early MPS, 6 additional patients were shown to have worsening of the reversible perfusion defects. Control angiograms revealed stent restenosis in all. In 23 patients (66%), MPS at 3 months were similar to early MPS. Then, worsening of MPS when compared to early findings was observed in 10 of 11 patients with new obstructive coronary lesions. 3 months after stenting, MPS findings remained unchanged in 23 symptom free patients.
Conclusion: 1 - Early MPS was improved in 80% of patients when compared to pre stenting MPS; 2 - Late worsening of myocardial scintigraphic perfusion defects when compared to early MPS has a very high predictive value for in-stent restenosis.

281 Tl-201 redistribution patterns early after primary stenting for acute myocardial infarction predict variable degrees of contractility recovery

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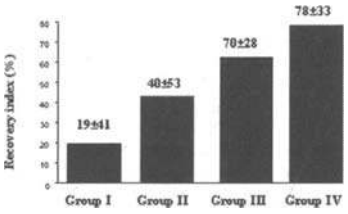
We sought to study the relationship between different redistribution patterns observed on stress-redistribution Tl-201 scintigrams (SPECT), early after successful reperfusion therapy for acute myocardial infarction (AMI), and late regional contractility recovery.

Patient characteristics

	Group I (n=8)	Group II (n=7)	Group III (n=21)	Group IV (n=5)	p
Age (y)	57±8	53±7	58±10	54±4	NS
Symptom to reperfusion time (min)	209±102	253±129	207±108	178±19	NS
Peak creatin kinase (IU/l)	4390±2452	2241±2452	1945±1848	1718±1284	0.03

Methods: We studied 41 consecutive patients with successful primary stenting for a first AMI and single vessel disease. All patients underwent dipyridamole stress-redistribution SPECT 6-10 days after the AMI followed within 24 hours by coronary angiography, showing absence of residual stenosis, and contrast ventriculography. Coronary and left ventricular angiography were repeated at 6 months follow-up. Regional wall motion recovery was assessed by contrast ventriculography.
Results: Early SPECT showed fixed defects in 8 (Group I), stress defects with rest redistribution in 7 (Group II), reverse redistribution in 21 (group III) and absence of defect in 5 patients (Group IV). There was a significant stepwise decrease in infarct size and increase in contractility recovery from group I towards group IV.



Contractility recovery

Conclusions: Late regional contractility recovery, after successful primary stenting for AMI, is predicted in a stepwise fashion by the analysis of early Tl-201 redistribution patterns.

282 Incomplete revascularization with coronary stenting in multivessel coronary disease: value of exercise myocardial scintigraphy

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Objectives: The aim of this prospective study was to evaluate, in patients who undergo a planned strategy of staged percutaneous coronary revascularization for multivessel coronary artery disease once stenting of the "culprit lesion" is performed, if the execution of an exercise myocardial scintigraphy might be able to predict those subjects with adverse events or need for further revascularization procedures.
Methods and results: In 146 patients (mean age 60±9 years) with multivessel coronary artery disease who underwent incomplete revascularization with coronary stenting from March 1997 to December 1999, an exercise 99mTc-tetrofosmin SPECT scintigraphy was performed prospec-tively 4 to 6 months after the revascularization procedure. Follow-up defined how time from scanning until a cardiac event (cardiac death, non fatal myocardial infarction and revascularization procedure), or patient response, lasted up to 45 months (median 15 months). A summed stress score, which takes into account the extent and severity of perfusion defects, was calculated to estimate the severity of perfusion abnormalities. Patients with normal scan were at low risk of cardiac events as compared to patients with abnormal scan (yearly event rate 0.6% vs 6.9%, respectively, p<0.05). Conversely no significant difference in cardiac events was observed when negative and positive exercise tests were compared (yearly event rate 3.5% vs 4.1%, respectively, p=NS). Statistical analysis using the Kaplan-Meyer survival curves showed a significant difference in event-free survival between patients with normal and abnormal scan (p<0.05). With the use of Cox proportional-hazards analysis, nuclear data provided significant incremental prognostic value for cardiac events (chi-square = 34.85), as compared to clinical (chi-square = 14.60), angiographic (chi-square = 19.73), and exercise test (chi-square = 24.06).
Conclusions: In patients with incomplete revascularization procedures exercise myocardial scintigraphy provides significant independent information concerning the subsequent risk of cardiac events, with an annualized event rate <1% for patients with a normal scan. Myocardial scintigraphy is able to predict better than exercise test alone, the occurrence of cardiac events and to provide incremental prognostic information after adjusting for clinical, angiographic and exercise variables.

283 Haemodynamic significance of in-stent lesions compared to native coronary lesions. A myocardial perfusion imaging study

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Background: Lesion complexity determines the hemodynamic relevance of a coronary lesion and in-stent lesions may be less complex than native lesions. This myocardial perfusion imaging study sought to determine whether the known relationship between severity of a native lesion determined by angiography and its hemodynamic impact can be translated to a in-stent lesion.
Methods: We identified 169 patients with single vessel disease and no wall motion abnormalities in the target vessel territory which underwent stress Tc-99m sestamibi single photon emission computed tomography within 2 months of angiography to determine the hemodynamic relevance of the lesion. 71 patients had a in-stent lesion and 98 patients had a native lesion. Coronary lesions were defined as hemodynamically relevant, if a reversible or partially reversible perfusion defect in the corresponding vessel territory was present on myocardial perfusion imaging.
Results: Reference diameters and lesion length were similar for stent and native lesions. The threshold diameter stenosis with the highest accuracy for detection of a hemodynamic relevant lesion was similar in both groups (stent: 58%, native: 59%). Receiver operator curve analysis yielded similar values for the area under the curve (0.87, 95% confidence interval (CI) 0.77-0.94 vs. 0.80, 95% CI 0.70-0.87, respectively). Considering the threshold values for the angiographic diameter stenosis the sensitivity and specificity to detect a hemodynamically significant stenosis was 91% and 85% for stent lesions versus 75% and 78% for native lesions. Multivariable analysis of lesion and stress imaging parameters yielded only diameter stenosis (odds ratio (OR) = 1.12, $p<0.001$) and lesion length (OR = 1.21, $p<0.01$) as independent predictors for ischemia during myocardial scintigraphy.
Conclusion: The threshold diameter stenosis of coronary lesions for reversible defects during stress myocardial perfusion imaging is similar for stent and native coronary lesions and is at least as accurate in stent lesions as in native lesions. Diameter stenosis and lesion length are the only predictors for hemodynamic relevance of a lesion while lesion type being native or in-stent is no independent predictor.

284 Magnetic resonance blood flow velocity after stent implantation

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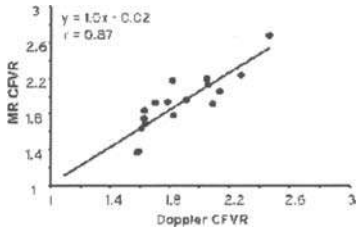
In patients with coronary artery stents a noninvasive visualization of the coronary arteries is not possible with magnetic resonance. Flow measurements may be an alternative having the additional advantage to allow the determination of functional significance, rather than anatomical alterations of a stenosis. Aim of the study was to determine coronary flow velocity reserve (CFVR) with MR in patients after stent implantation.
Methods: In 38 patients after successful PTCA and stent implantation flow velocity was determined at rest and under adenosine stumulation 5 mm distal to the stent using a phase contrast technique (Philips, ACS NT, 1.5 Tesla, prospective navigator triggering, TE/TR/flip:6.9/11.5/40, spatial resolution 1 x 0.9 mm, temporal resolution 45 ms). Measurements were repeated after 3 months and compared to invasive coronary angiography. In 18 patients additional invasive Doppler flow measurements were obtained.
Results: In 29 patients CFVR could be determined. After 3 months significant differences were found between coronary arteries with and without restenoses. Using a threshold of 1.5 for >50% stenoses and 1.2 for >75% stenoses a sensitivity of 85% (83%), specificity of 89% (94%), and diagnostic accuracy of 86% (90%) was reached. MR CFVR correlated well with the Doppler measurements (r=0.87).



MR flow reserve vs Doppler flow reserve.

Conclusions: The determination of coronary artery flow and flow reserve after stent implantation is feasible with magnetic resonance, correlates well with invasive flow measurements and allows to detect restenosis with high diagnostic accuracy.

285 Visualisation and assessment of stent patency using multislice spiral computed tomography (MSCT)

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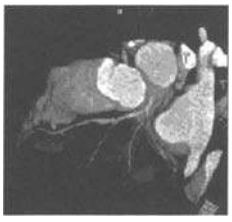
The present study aimed to assess the diagnostic value of MSCT in non-invasive evaluation of stent patency in comparison with conventional coronary angiography (CCA).
Material and Methods: We evaluated 49 patients (10 women, age 40 to 65 years, mean age 57 SD 10 years) with 51 stents in native coronary arteries. The patients were referred for CCA due to recurrent angina. One stent was implanted in the left main coronary artery, 28 in the left anterior descending artery (LAD), 15 in the right coronary artery, and 7 in the circumflex artery. MSCT scans (Somatom Plus 4 Volume Zoom, Siemens Erlangen) were obtained using Heart View software. Images were acquired throughout the entire cardiac cycle and then reconstructed at diastole with retrospective ECG gating. The stent was considered patent when contrast material was detected proximally and distally to the stent. MSCT scanning and coronary angiography were performed by two separate teams and were evaluated in a blinded fashion.
Results In 3 patients (6%) data acquisition with MSCT was not satisfactory (due to heart rate >65/min). In the remaining 46 patients (48 stents) - 3 stents (all in LAD) were identified as occluded, whereas 45 stents were found patent by MSCT. On angiography the same three stents were found occluded, and 45 stents were patent. The sensivity and specificity of MSCT in this group were 100%, respectively.



Stent in LAD 3D VRT.

Conclusion: As evidenced by our research MSCT may be a useful instrument in assessing the patency of coronary stents, although this technique should still be enhanced, with a view to facilitating an assessment of the inside of the stent (detection of in-stent restenosis). MSCT may be used efefctively for screening patients after stent implantation.

ADDING NEW DRUGS TO BASELINE TREATMENT IN HEART FAILURE

286 Acute haemodynamic effects of testosterone administration in men with heart failure

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Background: We have recently shown that testosterone administration may improve functional capacity in men with chronic congestive heart failure (CHF), in whom plasma testosterone levels may be relatively reduced. The mechanism of benefit is not clear but may include beneficial haemodynamic effects of testosterone. We have previously shown that testosterone acts as a vasodilator in-vitro in systemic, coronary and pulmonary arteries. The purpose of this study was to examine the acute effects of testosterone administration on central haemodynamics in men with CHF.
Methods: Nine male patients with stable CHF (mean age 61.9 ± 10.1years; ejection fraction 34.4 ± 12.6%) took part in a double-blind, placebo-controlled, cross-over study. In each subject, a balloon flotation catheter was passed into the pulmonary circulation and central pressures allowed to equilibrate for at least one hour. Subjects received 2 x 30mg tablets of testosterone or placebo via the buccal route. Heart rate, cardiac index and indices of left ventricular pre-load and after-load were recorded at t=0, 30, 60, 120, 180, 240, 300 and 360 minutes. Measurements were repeated the following day with the second test drug. The percentage change from baseline was determined at each time point. For each parameter, the mean of all changes from baseline in all patients was compared between active and placebo treatments, using paired t tests. Data are presented as % change from baseline (mean ± SD).
Results: At baseline, mean cardiac index was 2.98 ± 0.53L/min/m^2, mean pulmonary capillary wedge pressure (PCWP) was 12.3 ± 6.3mmHg, mean pulmonary artery pressure (PAP) was 23.4 ± 9.8mmHg. Active treatment produced a rapid rise in plasma testosterone from 11.4 ± 4.3nmol/L to a peak of 91.7 ± 39.1nmol/L. There was no apparent period effect, nor treatment-period interaction. There was no effect of testosterone on heart rate. Compared with placebo, there was a small reduction in both systolic and mean arterial blood pressure (-3.7 ± 9.7%, p=0.002; -3.5 ± 11.2%, p=0.01). In addition, there was a significant reduction in systemic vascular resistance (-9.8 ± 19.6%, p<0.001) and increase in cardiac index (+5.0 ± 12.9%, p=0.001). There was no effect of treatment on PCWP, PAP or pulmonary vascular resistance.
Conclusion: In male patients with CHF, acute administration of testosterone led to reduction in left ventricular after-load and augmentation of cardiac index, with no apparent effect on left ventricular pre-load. These haemodynamic effects may contribute to the clinical improvements seen in men with CHF treated with testosterone.

287 Effects of the addition of low dose of spironolactone on brain natriuretic peptide and cardiopulmonary function in patients with heart failure

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Low dose of spironolactone, in addition to standard therapy, reduces the cardiac mortality in patients (pts) with congestive heart failure (CHF).The objectives of this study were the evaluation if a low dose of spironolactone, in addition to standard therapy, might modify the plasma level of brain natriuretic peptide (BNP), the NYHA class and the cardiopulmonary (CP) function at CP test in pts with CHF.
Sixty-one CHF pts (39 males, mean age 59.7) underwent echocardiography, CP test and blood sample for BNP at the time of enrolment and after 6 months of spironolactone therapy. Pts were in NYHA I-III and left ventricular ejection fraction (LVEF) <40%. Plasma BNP concentration was determined by a use of a specific immunoradiometric assay (Shionora). The peak oxygen consumption (VO2) and the oxygen pulse (PO2) at CP test were analysed. The causes of CHF were due to: 23 (37.7%) coronary artery disease; 19 (31.1%) dilatative; 18 (29.5%) hypertension; and 1 other. Fifty-two (85.2%) subjects were treated with Angiotensin-converting-enzyme (ACE) inhibitor, 9 (14.8%) with blocking Angiotensin-II receptor, 27 (44.3%) with digoxin. All subjects had a loop of diuretic and 35 (57.3%) assumed carvedilol. The therapy was maintained stable during the study. The average dose of spironolactone was 30 mg/die. During the six months period 7 pts interrupted the study: 1 pt died a cardiac death, 1 pt had a myocardial revascularization and 5 pts for adverse effects. The results of BNP, LVEF, NYHA class, VO2 and PO2 are depicted in the table.
In conclusion low dose of spironolactone in addition to standard therapy reduced the BNP level in CHF pts (p=0.01) and improved LVEF (p=0.001). This therapy ameliorated the NYHA class (p=0.0001) without increasing the functional parameters (VO2 and PO2) at CP. test.

	Baseline	6-month follow-up	p
BNP (pg/ml)	45.7±57.3	18.6±26.8	0.014
LVEF (%)	28.8±7.6	36±10.8	0.001
NYHA class	2.2±0.58	1.7±0.5	0.0001
VO2 (ml/kg/min)	17±5.8	17.4±5.3	0.64
PO2 (ml/b)	9.1±4.4	9.7±3.6	0.36

288 Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in chronic heart failure patients

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Background: in severe chronic heart failure (CHF) spironolactone administration(SP) improves survival, but the underlying mechanisms are still not fully understood. We aimed to assess whether SP may affect left ventricular (LV) function and exercise tolerance in CHF patients. Methods: we prospectively studied 106 outpatients with CHF. Patients were randomized to treatment with SP, titrated up to 50 mg/die (group 1) or control group (group 2). A complete echocardiography and a cardiopulmonary exercise testing with measurement of peak oxygen consumption (VO2) were performed at baseline and 12 months after randomization. Results: LV end-systolic volume at baseline and at follow-up was 188±94 mL and 171±97 mL in group 1 and 173±71 mL and 168±79 mL in group 2,respectively, p=0.03 for treatment group-by-time interaction). LV ejection fraction at baseline and at follow-up was 33±7% and 36±9% in group 1 and 34±7 and 34±9 in group 2,respectively, p=0.02 for treatment group-by-time interaction). At baseline, 9 patients in group 1 and 3 in group 2 had a restrictive mitral filling pattern,a marker of severe diastolic dysfunction; at follow-up, three patients in group 1 and no patient in group 2 improved the pattern; no patient in group 1 and four patients in group 2 worsened the pattern (chi-square test, p =0.02). Peak VO2 significantly increased in patients treated with 50 mg of spironolactone and decreased in group 2 (17.7±5.2 vs. 18.5±5.9 and 19.1±5.6 vs. 17.9±5.3, respectively; ANOVA: p=0.01). Conclusions: SP administration in chronic heart failure patients decreases LV volumes and improves LV systolic and diastolic function; furthermore, it improves exercise tolerance at the highest administered dose. Our data might help to explain the reduction in mortality observed during aldosterone antagonism in CHF patients.

289 Hyperkalemia and impaired renal function during treatment with spironolactone in patients with heart failure: figures from a real world scenario

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Background: Treatment with Spironolactone (SPL) is beneficial in patients with severe congestive heart failure (CHF). In the RALES-trial SPL was well tolerated, particularly with regard to renal function and serum-K$^+$ levels.
Aim: To investigate whether the reported low frequency of adverse effects during SPL treatment in a heart failure population could be confirmed in an unselected heart failure outpatient cohort.
Methods: We investigated 125 consecutive patients with CHF recruited from our heart failure clinic. Inclusion criteria were LVEF <45% and treatment with SPL. Mean age was 72.9 yrs (range 46.5-90.6), 27.4% were women. NYHA-class distribution was: I: 5.7%; II: 43.9%; III: 46.3% and IV: 4.1%. Mean EF was 28.8±4.5%. Other medications included ACE-I in 64.0% and betablockers in 32.8%. Blood tests were performed bimonthly or more frequently if necessary.
Results: At baseline (BL) creatinine levels were 117.4±6.5 (mean±SD; μmol/l, normal <130) and serum-K$^+$ was 4.1±0.3 mmol/l. The mean follow-up period was 11 months, and the cumulative observation period was 73 SPL treatment yrs. Mean peak s-creatinin was 160.2 μmol/l (36.5% incr. from BL) and mean peak s-K$^+$ was 4.89 (16.2% incr. from BL). 60 pts. were already on SPL when admitted to the CHF clinic, with >30% receiving >25 mg/d. The remainder were initiated on SPL, with 9% receiving a dose >25 mg/d. During the follow-up period a total of 30.4% of the pts. developed hyperkalemia (>5 mmol/l), with 4.8% having serum-K$^+$ >6 mmol/l. 46.4% of all patients had an increase of s-creatinine of >20%, and 17.6% increased >50%. These alterations in s-creatinine and serum-K$^+$ were not significantly more frequent in patients treated with ACE-I or betablokkers or high-dose SPL (>100 mg/d).
Conclusion: SPL adverse effects (impaired renal function, increase in s-K$^+$) are much more prevalent in our elderly CHF patient population than previously reported. Care should be given to the continuous monitoring of electrolytes and renal parameters.

290 Effects of pentoxifylline in severe heart failure

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Background: Patients with severe (NYHA FC IV) heart failure have a more than two-fold increase in cytokine concentrations in comparison to patients with moderate heart failure. Whether pentoxifylline (a drug known to modulate cytokines as TNF-alpha, IL-6, IL-10 and Fas/Apo-1) modifies the marked changes in cytokines that occur in severe heart failure has to be determined.
Methods: In a prospective, randomised, double blind, placebo controlled study we enrolled 18 consecutive patients with idiopathic dilated cardiomyopathy in FC IV. All patients required admission to intensive care unit for at least 7 days and intravenous inotropic support. Patients were randomised to pentoxifylline (400 mg TDS) or placebo in addition to diuretics, digoxin and ACE-inhibitors. Echocardiograms, radionuclide studies, TNF-alpha (in pg/ml) and Fas/Apo-1 (an apoptosis signalling receptor; in U/ml) plasma concentrations were determined on admission and after 1 month of treatment.
Results: There were no differences in baseline characteristics between the 2 study groups. Baseline ejection fraction of the study population was 16.8±8%, and baseline plasma levels of TNF-alpha and Fas/Apo-1 were 19.0±12pg/ml and 17.0±8U/ml. These levels were significantly higher compared to the concentrations we found previously in patients in FC II-III ($p<0.001$ for both). After one month 3 patients died (2 in the placebo group). There was a significant reduction in the TNF-alpha (16.7±3 to 8.0±2pg/ml, $p<0.05$) and Fas/Apo-1 (15.2±1 to 9.6±2 U/ml, $p<0.05$) plasma levels in the patients treated with pentoxifylline with no significant changes in the placebo group. This was associated with a significant increase in ejection fraction in the pentoxifylline group (16.6±6 to 24.4±4, $p<0.05$).
Conclusion: In patients with severe heart failure treatment with pentoxifylline is associated with a decrease in TNF-alpha and Fas/Apo-1 plasma levels and improvement in systolic performance compared to placebo. However, higher dose of pentoxifylline may be required to fully suppress the TNF-alpha and Fas/Apo-1 plasma levels.

291 Beneficial effects of short-term inotropic support on clinical status and on adrenergic drive in patients with severe congestive heart failure

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Background: Short-term administration of inotropic support decreases symptoms and signs of congestion in patients with decompensated congestive heart failure (CHF). It is unknown how these agents affect norepinephrine (NE) and functional capacity early (3 days) and late (30 days) after treatment. The objective of this study was to investigate the effects of milrinone (M) or dobutamine (D) on clinical status, functional capacity measured by a 6-minute walking test, plasma NE and troponin T (TnT) levels in patients with CHF and class IIIb or IV symptoms requiring inotropic support.
Methods: Forty patients with decompensated heart failure for a mean duration of 12±12 days [median=10 days, NYHA class 3.8±1.2 (mean ± SD); LVEF=24±8% were randomly assigned to receive M [0.6±1.0 μg/kg/min] or D [9±2 μg/kg/min] for 72±29 hours. All patients received triple therapy (digitalis/ACE inhibitor/diuretics) and 6 (15%) received a beta-blocker. Plasma NE and TnT levels were measured before the initiation of inotrope, 24 hours post-inotropic support, and 30 days later. A 6-minute walk-test was performed 24 hours post-treatment with M or D and at 30 days.
Results: Both M and D improve NYHA class at 3 days (2.5±7) and 30 days (2.7±0.7); ($p<0.05$ versus baseline). Six-minute distance walked improved significantly from 3 days (237±96 meters) to 30 days (309±91 meters); $p<0.001$. There was a trend in favor of M ($p=0.09$). Plasma NE decreased from 749±349 (BSL) to 659±432 (3 days), and 594±487 (30 days); $p<0.001$. The changes in NE overtime was similar for M and D. TnT were slightly elevated at baseline [0.2±0.3 mcg/L] but did not change significantly at 3 and 30 days in response to inotropes.
Conclusion: Short-term administration of D or M provides clinical, functional, and neurohumoral benefits which persist and even increase at 30 days. M and D appear equally efficacious in this cohort of patients with low use of beta-blockers and severe disease.

CURRENT INITIATIVES IN CARDIAC SURGERY IN THE MANAGEMENT OF HEART FAILURE

292 Partial left ventriculectomy has favourable effects on myocardial morphology one-year postoperatively: a semiquantitative morphometric study

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In order to assess histological changes of the LV myocardium one-year following partial left ventriculectomy (PLV) we compared, in semiquantitative fashion, major morphometric parameters in the LV specimens taken during surgery and endomyocardial biopsies (EMB) one-year postoperatively. The study group consisted of 12 consecutive PLV survivors, who were predominantly male (10/12), aged 46+12 years. Surgical operative specimens were taken from the infero- and/or posterolateral wall of the LV, processed routinely and stained with Masson-trichrome for better contrast. Postoperative LV EMB, 3-5 per patient, were taken 12 months later and processed in exactly the same manner. The following morphometric parameters were assessed: (1) degree of hypertrophy and. attenuation of myocardial fibres (diameter); (2) nuclear evidence of hypertrophy (diameter); (3) myofibrilar volume fraction; (4) degree of degenerative, vacuolar changes in cardiomyocites, and (5) fibrosis volume fraction. These parameters were assessed semiquantitatively and graded in usual fashion (0-none, 1-mild, 2-moderate, and 3-severe). Myofibrilar hypertrophy and attenuation, as well as fibrosis and myofibrilar volume fraction, were interexclusive (mutual score was maximum 4).
Results: Both NYHA class and EF were improved 12 months following operation as compared to preoperative values (2.25±0.45 vs. 3.33±0.69, $p<0.001$, and 34±10% vs. 21±9%, $p<0.001$, respectively). Semiquantitative morphometric analysis demonstrated postoperative decrease in the degree of myofibrilar attenuation as compared to preoperative values (1.50±0.52 vs. 2.42±0.67, $p<0.01$), as well as postoperative decrease in fibrosis volume fraction (2.08±0.79 vs. 2.67±0.49, $p<0.01$) and consequent increase in myofibrilar volume fraction (1.92±0.77 vs. 1.33±0.49, $p<0.01$). There was no difference in post- and preoperative degree of myofibrilar hypertrophy, nuclear evidence of hypertrophy, and degenerative changes in myocardial fibres (1.17±0.39 vs. 1.25±0.45, 1.33±0.49 vs. 1.67±0.65, and 1.50±0.52 vs. 1.83±0.83, respectively).
Conclusions: One-year postoperatively, PLV has favourable effects on myocardial morphology, that parallels improvement in patient's functional status and LV systolic function. Histological remodelling is mainly due to the decrease of attenuation (reduced LV dilatation), increase of the relative myofibrilar volume fraction, and decrease of the fibrosis volume fraction.

293 Effects of surgical reduction in left ventricular size on left ventricular systolic and diastolic function

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Reduction in left ventricular size by excluding the noncontracting dyskinetic or akinetic segments, combined with coronary artery bypass grafting (CABG), is a surgical technique that can be utilized in the treatment of patients (pts) with a remodeled dilated ventricle after anterior myocardial infarction (AMI). The aim of this study was to evaluate the effects of this technique on the preoperative and postoperative NYHA functional class, left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and early filling/atrial filling wave peak velocity (E/A) ratio in pts with postinfarction dilated cardiomyopathy. We studied 55 pts (51 men, 4 women), mean age 64 years (range 39-82) with previous AMI and dilated cardiomyopathy who underwent operation (Guilmet's procedure in 44 pts and Dor's procedure in 11 pts) between September 1998 and September 2001, and were followed for 18 months. Mitral repair was used in 4 pts and mitral replacement in 3 pts. The parameters of ventricular function were determined through two-dimensional and pulsed Doppler echocardiography before operation, at disharge, at 6 months in 71% of pts and at 18 months in 51% of pts. For the statistical analysis of the data Student's t test for paired data was used. Overall hospital mortality among 55 pts was 3.6% (2 deaths). Follow-up at 18 months revealed 8 late deaths (5 sudden deaths and 3 deaths from progressive pump failure); overall survival at 18 months was 81.8%. In 15 pts (33%) an improvement of the NYHA class was observed at follow-up (2 pts from NYHA III to NYHA I, 3 pts from NYHA III to NYHA II; 10 pts from NYHA II to NYHA I). A significant increase in the LVEF was observed in the evaluation at disharge, at 6 months and at 18 months (from the preoperative LVEF 33+8% to 38+8% at disharge, $p<0.001$; 39+9% at 6 months, $p<0.001$; and 39+9% at 18 months, $p<0.005$, respectively). A significant reduction in the LVEDV was observed in the evaluation at disharge, at 6 months and at 18 months (from the preoperative LVEDV 143+30 ml to 96+18 ml at disharge, $p<0,001$; 104+23 ml, $p<0,001$ at 6 months; and106+31 ml at 18 months, $p<0,001$, respectively) without any E/A ratio change. In conclusion, our data demonstrate that a surgical reduction in left ventricular size, combined with CABG, determines a significant improvement in LVEF without any left ventricular diastolic function change and is associated with low operative mortality. The high incidence of sudden death at late follow-up indicates the need for the identification and treatment of high risk patients.

294 Surgical revascularisation in patients with ejection fraction lower than 30%: experience in over 2000 patients

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Material and methods: During the past 18 years 2007 patients (19%) with ejection fraction lower than 30% underwent myocardial revascularization. There were 1795 male and 212 female patients with the average age of 54.8 years. The majority of the patients (56%) had previous myocardial infarction on anterior wall, 28% on the posteroinferior, and 15% on both walls.
Results: The postoperative 30-day mortality in the whole group of 2007 pts was 3.8%.The majority of them died due to cardiac causes. There were 1044 pts (52%) who underwent coronary arteries endarterectomy (E) due to poor distal coronary bed. E was performed on one vessel in 688 pts (66%), on two coronary arteries in 288 pts (27%) and on 3 vessels in 68 pts (6%). Postoperative mortality in this group of 1044 pts was 4.5%. In order to prevent early thrombosis after coronary endarterectomy, we introduced in 1988 Prostacyclin as anticoagulant, antiaggregation therapy and bridge to heparinisation. Using Prostacyclin we reduced the perioperative infarction rate to 7.5%.
Conclusion: Contrary to certain authors' opinions, we believe that poor distal coronary bed is not a contraindication for myocardial revascularisation, even in patients with failing left ventricle (ejection fraction lower than 30%). However, we think that this technique enables a new chance for helping this group of patients and extends indications for myocardial revascularisation.

295 The extent of akinetic myocardium predicts in-hospital mortality after left ventricular endoaneurysmorrhaphy

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Introduction: Endoaneurysmorrhaphy [EAR] has become an important therapeutic strategy in the treatment of patients with left ventricular [LV] aneurysm and congestive heart failure. However, little is known about risk factors for early mortality.
Material and Methods: We reviewed our experience with 147 patients with antero-septal LV aneurysms undergoing EAR. 70% of the patients were male; mean age was 62±9 years. The 30° RAO view of the preoperative LV cineangiograms was analyzed using software that allows manual tracing of the LV outlines. Data on regional LV function were derived using the centerline method. Absolute ventricular volumes were obtained using the Area Length method and then normalized for body-surface area. Demographic, hemodynamic, angiographic and surgical variables were analyzed in order to determine risk factors for in-hospital mortality.
Results: 133 patients had additional bypass surgery, 1 had additional mitral valve replacement. In-hospital mortality was 4.1% (n=6). Risk factors for in-hospital mortality were: the extent of akinetic myocardium (given in percent of the total LV-circumference; p=.027) and the duration of cardiopulmonary bypass (p=.0068) which was itself dependent on the LV-ejection fraction (p=.001), the number of stenosed coronary arteries (p=.004), and the extent of akinesis (p=.023).
Conclusion: Endoaneurysmorrhaphy can be performed with acceptable perioperative results. The risk of perioperative mortality was higher among patients with a larger extent of akinesis. Akinesis may increase in many patients over time; thus,our finding highlights the importance of optimal timing of the surgical intervention.

296 Autologous skeletal myoblast transplantation in treatment of postinfarction heart failure – phase I clinical trial feasibility study

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Congestive heart failure secondary to myocardial infarction (MI) continues to be a major complication, despite advances in its treatment in the acute phase. The loss of cardiomyocytes is inversely related to the cardiac output and pressure-generating activity and subsequently leads to ventricular remodeling. The cardiomyocytes lost during MI cannot be regenerated and this affects the quality of life and survival. Experimental data suggest that myogenic cell grafting into area of postinfarction injury is a promising approach to the treatment of heart failure but transplantation of fetal cardiomyocytes raises availability and ethical issues. Transplantation of autologous skeletal myoblasts (ASM) has been evidenced by experimental data and suggested by initial clinical observations to improve both systolic and diastolic function after MI. Therefore we have established a Phase I clinical trial to evaluate the use of ASM transplantation performed during coronary artery bypass grafting (CABG) by non-profit research and academic institutions. Survivors from MI scheduled for CABG, with an akinetic area of the left ventricle, were screened by means of dobutamine stress echocardiography and included into the study when no viable myocardium was detected. In seven patients up to date, the skeletal myocardial biopsy was obtained from vastus lateralis. After isolation the cells were cultured for three weeks and up to 2x107 myoblasts per patients were grown. Myoblast injection into the akinetic area was done after constriction of the anastomoses during CABG procedure. No major perioperative complications were observed and an increase in segmental contractility was seen during initial 4 and 8 weeks visits. We conclude that ASM transplantation for treatment of postinfarction heart failure is feasible and initial observations justify further research to validate the method and define its role in clinical practice.

297 Medium-term prognostic evaluation of patients with symptomatic left ventricular aneurysms after endoventricular reconstructive surgery

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Objective: Endoventricular reconstructive surgery (EVRS) for treatment of postinfarct ventricular aneurysms leads to excellent short-term results. However, only sparse data of medium-term response after EVRS are currently available.
Methods: EVRS was performed in 171 patients (62 ± 9 years) with symptomatic ventricular aneurysms (median NYHA functional class III, EF mean 36±5%). Clinical and surgical variables influencing cardiac mortality and morbidity during follow-up were determined by univariate and multivariable analysis.
Results: Perioperative mortality was 5.7%. Mortality during follow-up was 3.8% per year, resulting in a 5-year survival rate of 78%. The NYHA status improved significantly during the follow-up period (median NYHA II; $p<0.001$, EF 46±9; $p<0.05$). Multivariable analysis only identified preexisting peripheral arterial occlusive disease ($p= 0.048$) as a significant factor influencing medium-term mortality.
Conclusions: Endoventricular reconstructive surgery entails low perioperative mortality, results in significant clinical improvement and is associated with low medium-term cardiac mortality and morbidity. The extent of generalized arterial occlusive disease should influence the therapeutic strategy for patients with symptomatic ventricular aneurysms.

PROGNOSIS IN HEART FAILURE: PREDICTORS OF OUTCOME

303 Optimisation of medical treatment in severe heart failure patients in tertiary care centers: benefit on hospitalisation rate

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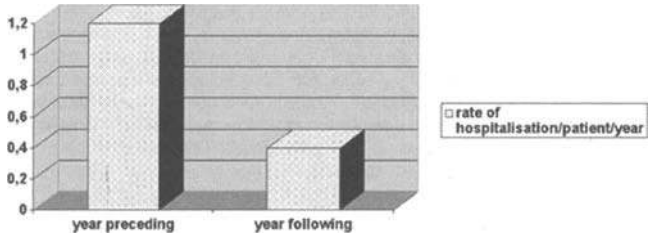
Background: congestive heart failure (CHF) is responsible for multiple hospitalisations. The aim of this study was to evaluate the benefit of optimisation of therapy by tertiary centers on hospitalisation rate in severe CHF patients addressed for heart transplantation (HT).
Methods: 62 patients were referred for HT from 1/1992 to 1/2000. All had been managed by at least 3 cardiologists (in and out hospital) who felt that therapy was optimal.
During hospitalisation in our center, modification of therapy included adaptation of diuretic dosage, increase in ACE inhibition and beta-blockade according to ESC recommendations. Besides, all patients benefited from an individualized dietetic information and information on their disease.
We compared the number of hospitalisations during the year before and after modification of treatment.
Results: Patients were 50±11 y.o.(22-69), LVEF was 24±12%, cardiac index 2.2±0.6 l/min/m^2, VO2 was 16.4±5.2 ml/kg/min, i.e. 53±17% of theoretical value, and hyponatremia was present in 34% of the patients.
ACEI could be introduced in 7 (11%) deemed intolerant, and dosage was increased from 44 to 63% of the recommended dose in the others. 37% instead of 13% received full dose at the end of the stay ($p<0.001$). Beta-blockers were introduced in 7 (11%) patients, mean dose was 37% of recommended dose. Furosemide was decreased from 98 to 88 mg/d and spironolactone from 64 mg to 35mg (the number of patients receiving 25mg increased from 23% to 53%).
The rate of hospitalisation per year per patient decreased from 1.2 to 0.4 ($p<0.001$ fig).



Rate of hospitalisations.

Conclusion: Optimisation of heart failure treatment significantly decreases the rate of hospitalisation. However, in severe patients this appears to be possible only in highly trained centers.

304 Mortality in left ventricular dysfunction treated with angiotensin-converting enzyme inhibitors. Ten-years follow-up post SOLVD close out

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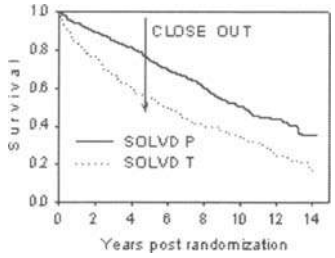
To evaluate the impact of ACE-Inhibitor (ACE-I) therapy on the cause of death in patients with left ventricular dysfunction (LVD), 433 patients of the Belgian cohort were treated with open label ACE-I after the close out of the Studies Of Left Ventricular Dysfunction (SOLVD). 97 and 336 survivors respectively included in the Treatment (T, NYHA II-III, mean EF:24%) and Prevention (P, NYHA I-II, mean EF:29%) arms of the SOLVD were followed up during 10 years (from Feb 91 to Feb 01). The etiology of LVD was ischemic heart disease in 79%, idiopathic cardiomyopathy in 14% and other, such as valvular disease, in 7%. No patients were lost to follow-up. By Feb 01, 237 patients (55%) had died, 64 in the T group (66%) and 173 in the P group (51%). The causes of death were classified based on ICD-9 codes. 82% of patients (195/237) died from cardiovascular (CV) causes. The mode of CV death was: pump failure, n=82, sudden death/arrhythmia, n=78, myocardial infarction, n=13, cerebrovascular accident, n=15, following cardiac surgery, n=6 and pulmonary embolism, n=1. In addition, 12 had heart transplant. The primary cause of non-CV death was cancer (n=27) particularly lung (n=10), digestive tract cancers (n=6), urinary cancer (n=3) and breast cancer (n=2). At the end of the SOLVD follow-up, the treatment received included ACE-I (78%) or AII receptor blockers (6%), beta-blockers (27%), aspirin (58%), diuretics (31%) and antiarrhythmics (24%).
In conclusion, our data indicate that serious CV events still drive mortality in



SOLVD follow-up.

patients with LVD treated with ACE-I. More research, targeting specific mechanisms of death, particularly sudden death, is needed to improve the prognosis particularly in patients with asymptomatic systolic LVD.

305 Survival following first hospitalisation with heart failure in Leicestershire 1993–2001

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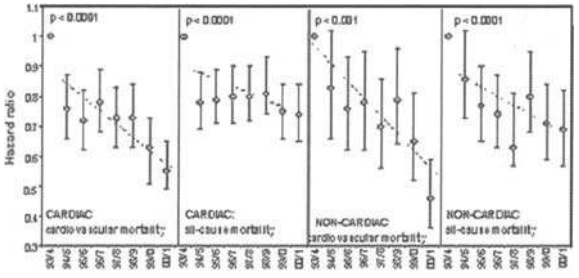
Rates of first hospitalisation for heart failure increased steadily in the 1980's-early 1990's. We used record-linked data to study temporal trends in incidence of and survival following first hospitalisation with heart failure in Leicestershire (population 1 million),1993-2001.The influence on survival of demographic factors and comorbidity were studied. From March 1993-April 2001, 12,200 individuals had first hospitalisation with heart failure. In these the primary diagnosis was cardiac in 8,302, non-cardiac in 3,918. Annual numbers rose from 1,100 (29/10,000 population) in 93/4 to 1,920 (47/10,000) in 2000/1. Only 27% had been hospitalised previously with a recognised precursor of heart failure.Mean follow-up was 507 (range 0-3,072 days). 4,971(60%) of the cardiac cohort died by the end of follow-up, 3,643 from cardiovascular causes. Hazard of death increased by 45% for each 10 years of age and was 15% greater for males. Concomitant MI was linked to lower survival. There was no association of social deprivation or diabetes with outcome. From 1993-2001 overall in-hospital mortality did not change (25-21%,p=0.15), but a trend to improvement was seen in the cardiac cohort (23-15%, p=0.05). From 1993/4 -2000/1, post-discharge survival by 50% improved in the cardiac cohort(X^2=13,$p<0.001$ all cause; X^2=32, $p<0.0001$ cardiovascular mortality) with similar trends in the non-cardiac cohort (Fig). We observed no improvement in survival for patients (n=1195) with concomitant MI (X^2=1.2, p=0.28).



In the modern treatment era, rates of and mortality after first hospitalisation with heart failure remain high. However clear trends to improving survival are apparent over the period 1993-2001.Improving survival and high incidence has implications for the prevalence of heart failure.

306 BMI as independent predictor of increased mortality in patients with multiple coronary risk factors: 3-year follow-up

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Objectives: Nowadays, recent studies have shown that obesity is not associated with increased mortality in pts with CHF, and may confer a more favorable prognosis. Similar findings have been reported recently in older pts with hypertension and without CHF. This study aimed to evaluate the role of body mass index (BMI) in the prognosis of 203 consecutive patients with multiple risk factors, but without signs of congestive heart failure. Methods: From January 1997 to January 2001 we prospectively studied 203 consecutive pts (105 males, 97 females, mean age 68.7±8.8y) examined in an outpatient cardiology unit. The pts were subclassified into four categories of BMI defined as: B-1 (BMI 19-25 kg/m^2), n=55, mean BMI 22.2 ± 1.26; B-2 (BMI > 25 and < 29 kg/m^2), n= 65, mean BMI 26.6 ± 0.9; B-3 (BMI = or > 29 and < 32 kg/m^2), n = 46, mean BMI = 29.9 ± 1.0 and B-4 (BMI = or > 32 kg/m^2), n=36, mean BMI = 34.7 ± 2.7. Univariate and multivariate analyses were performed to test the association between body mass index and 3-year mortality and morbidity. Results: The four groups had similar profiles in terms of risk factors (hypertension, diabetes mellitus, serum cholesterol), the presence of CAD, stroke and atrial fibrillation. Lean pts were significantly younger compared to overweight and obese pts (p=0.05). During follow-up 62 (30%) pts died: 27 (13%) pts in B-1, 15 (7%) pts in B-2, 8 (4%) pts in B-3, 10 (5%) pts in B-4, (p=0.005). Using a Kaplan-Meier survival curve model there was a 40% increase of total mortality in group B-1 compared to group B-3 and 34% increase in group B-1 compared to group B-2 (log rank=17.8, p=0.005). After adjusted multivariate Cox proportional-hazard analysis, age (OR 1.12, p=0.0001, 95% CI 1.08-1.16) and BMI category (B-1 compared to B-3: OR 2.8, p=0.01, 95% CI 1.15-2.56), B-1 compared to B-2: OR 2.6, p=0.05, 95% CI 1.03-2.32) and B-1 compared to B-4: OR 2.5, p=0.05, 95% CI 1.40-3.45) were the only independent predictors of increased mortality. Conclusion: Among pts with multiple risk coronary factors, overweight status was associated with decreased total mortality compared with lean subjects. Further studies are needed to clarify this seemingly unexpected finding.

307 Prognosis of congestive heart failure in the middle-aged and elderly population in a urban population segment of Copenhagen

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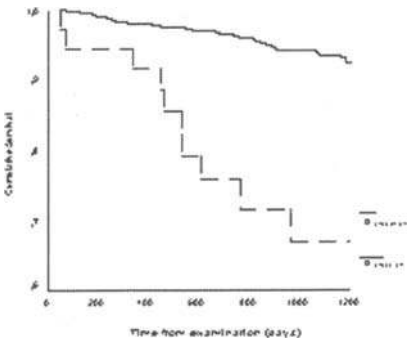
Background: The purpose of the study was to determine the prognosis, total mortality and cardiac morbidity, of patients with LV systolic dysfunction and heart failure (CHF) in the general population.
Methods: A total of 764 subjects(56,5% female), aged 50-89 years participated in the study recruited from GP's. Each participant filled in a CHF questionnaire, ECG, blood tests and echocardiography were performed.
Results: Median follow-up was 1145(range:51-1197) days. Survival first and second year after the examination was 91.7%, and 76.5% in subjects with LVEF≤40%[age controlled mortality rate 4.6(95% C.I.=1.6-13.2)] compared to 97.9%, respectively 96.8% of those with LVEF>40%.
In Cox proportional hazards analyses age, gender, history of hypertension, history of IHD, diabetes, dyspnoea, ankle edema, heart rate, systolic and diastolic blood pressures, abnormal ECG, LVEF≤40% were evaluated as potential prognostic factors for mortality and admission for CHF. LVEF≤40%(hazard ratio (HR)=3.72, p=0.0004), admission for ankle edema(HR=3.81, p=0.0006), male gender(HR=2.55, p=0.002) and age(HR=1.08 per year, p<0.0001) were independent predictors of total mortality. LVEF≤40%(HR=4.14, p<0.009), admission for pulmonary congestion(HR=7.80, p=0.0001), CAD(HR=4.93, p=0.002) and age (HR=1.11 per year, p=0.0004) were independent markers for CHF admissions. All-cause mortality (27.8% vs. 5.6% deaths, p<0.0001), first CHF admissions (25.0% vs. 1.9%, p<0.0001), and for other cardiac causes (25.0% vs. 6.3%, p<0.0001) were significantly higher in subjects with LVEF≤40% than in subjects with LVEF>40%.
Conclusion: In this large sample of the general population, patients with LV systolic dysfunction had a poor prognosis for total mortality as well as for cardiac morbidity.



Kaplan-Meier plot of cumulative survival.

308 Prognosis of heart failure in the general population – results from the London heart failure studies

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The prognosis of incident (new) cases of heart failure arising from the general population in the modern era is not well described. We report the results of follow-up of a large cohort of incident cases of heart failure in London, UK.
Methods: Between April 1995 and March 1998, 552 incident cases of heart failure were identified in the Hillingdon and Bromley Heart Failure Studies from populations of 150 000 and 195 000, respectively. The design of both studies was identical. Cases were identified from acute admissions to the hospitals serving the two areas, and from a rpaid access clinic to which suspected cases of heart failure were referred by the primary care physicians recruited to the study. The clinical assessement, ECG, chest radiograph and echocardiograpm of all cases were reviewed by a panel of 3 cardiologists (DAW, AJSC, GCS) working to a pre-set definition of heart failure according to the European Society of Cardiology guidelines. The combined cohort of 552 cases has now been observed for a minimum of 3.5 years (90% range 3.6 to 6.1 years) with automatic notification of death from the Office of National Statistics.
Results: The combined cohort included 196 men and 256 women, with a median age of 76 years. During the follow-up period 324 (59%) subjects have died. Survival was 84% at 1 month, 74% at 6 months, 69% at 1 year, 60% at 2 years, 51% at 3 years and 43% at 4 years (Kaplan-Meier method) Age, smoking status, NYHA class, systolic blood pressure, serum creatinine and LV systolic function were associated with survival on Cox univariate analysis. Cases in whom coronary artery disease was the aetiology had a poorer survival than the remainder (Hazard Ratio 0.79 [95% Confidence Interval 0.63-0.99] P=0.04). Cases identified as inpatients had approximately twice the mortality risk of those identified in the clinic (HR 2.18, 95% CI 1.66-2.86 P<0.001).
Conclusions: The average life expectancy of a new case of heart failure arising in the general population is 3 years, with the highest risk of death in the first 3 months. Simple clinical features can be used to identify those with the poorest prognosis.

REFINED DOPPLER INDICES FOR ASSESSING DIASTOLIC FUNCTION

324 Non-invasive estimation of left ventricular end-diastolic pressure by pulmonary venous flow deceleration time

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Aims: The scope of this study was to assess the potential value of pulmonary venous flow diastolic deceleration time (PVFd-dt) to predict end-diastolic pressure and stratify patients with regard to elevation of left ventricular end-diastolic pressures (LV-EDP).
Methods and results In 176 consecutive patients without mitral valve disease or atrial fibrillation PVFd-dt was determined by transthoracic Doppler and compared to LV-EDP measured invasively during cardiac catheterization. The sample was randomly divided into two subgroups of equal size for modelling of prediction and independent testing of the model.
Results: Predicted LV-EDP calculated from PVFd-dt (LV-EDP =-10.87+5261/PVFd-dt) agreed well with measured LV-EDP (mean difference: -1.3±3.4 mmHg). The correlation of LV-EDP with PVFd-dt is fair (r=0.73989). A value of PVFd-dt <220 ms is suggestive of elevated LV-EDP and should be monitored. A value of PVFd-dt <190 ms predicts elevated LV-EDP. A value of PVFd-dt <165 ms predicts severely elevated LV-EDP. With 190 ms as a cut-off value for elevated and 165 ms for severely elevated LV-EDP cross-table analysis classifies all patients with normal LV-EDP correctly. No patient with severe elevation (<18 mmHg) of LV-EDP is classified as normal (Chi^2=102, P<0.0001).
Conclusion: PVFd-dt is an appropriate non-invasive measurement to stratify patients with respect to potential elevation of LV-EDP.

325 The importance of late left ventricular diastolic filling wave propagation in assessment of diastolic dysfunction

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Background: Pulsed Doppler indices of both transmitral and Pulmonary vein flow present a parabolic distribution during progression from normal to advanced diastolic dysfunction (DD). Color M-Mode Doppler displays velocities data along a scan line and early transmitral velocity propagation (Ep) throughout the left ventricle (LV) has been proposed as a useful non-invasive index for assessing LV relaxation. However, there is no data concerning the importance of late transmitral velocity propagation (Ap).
Methods: We investigated 100 patients aged 58,5 ± 10 years who presented to our laboratory with echocardiographic evidence of LV diastolic dysfunction. Fifty pts had delayed relaxation (Group I) and 50 patients (pts) pseudonormal pattern (Group II). Forty age-matched, healthy persons served as a control group (Group III). An echocardiography study and colour M-Mode Doppler from the apical 4-chamber view in LV inflow, was performed and delayed relaxation pattern was defined if early (E) to late filling wave (A) was <1, isovolumetric relaxation time (IVRT) was >100msec, deceleration time of E (DTE) was >220 msec and atrial component (AR) of the pulmonary vein flow was <35 cm/sec. Pseudonormal pattern was recognized if E/A=1-2, DTE=150-200msec, IVRT=60-100 msec and AR>35 cm/sec.
Results: In pts with DD, the Ap slope was steeper than Ep compared to the normal group. The table shows the differences between the three groups.

	LVEF(%)	LA(mm)	E/A	AR(m/sec)	Ep(m/sec)	Ap(m/sec)
Group I	49±14	39,1±5,0	0,6±0,1	0,32±0,02°	0,40±0,09°	1,05±0,27°
Group II	43±15°©;	42±5,5°†	1,6±0,5	0,4±0,03°©;	0,32±0,07°	1,11±0,49°
Group III	52±10	37,8±3,8	1,11±0,4	0,20±0,03	1,09±0,27	0,67±0,1

° = p<0,05 vs Gr.III † = p<0.05 vs Gr I

Conclusions: Pts with DD reveal a reverse relationship between early and late filing propagation through the LV with the slope of Ap showing more oblique angle, compared with normal pts. Estimation of Ep and Ap slopes may help to diagnose the existence of diastolic dysfunction, especially in the presence of pseudonormal pattern were there are difficulties in the clinical setting to ungroup from normal.

326 Value of Doppler tissue imaging to predict left ventricular filling pressure in patients with CAD

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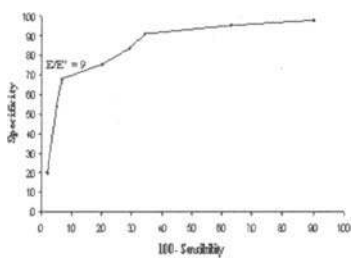
Background: Doppler Tissue Imaging (DTI) has been proposed to assess left ventricular (LV) filling pressure. The aim of this prospective study was to investigate reliability of this method in patients with CAD in clinical practice.
Methods: We studied 32 consecutive CAD-patients, mean age 64 ± 12 years, in sinus rhythm. All patients underwent cardiac catheterization and echocardiography in the same hour. Cardiac catheterization was performed with ventriculography and measurement of pre-A-wave pressure. The following Doppler echocardiographic parameters were assessed: 1) Pulsed wave Doppler signals from the mitral inflow (E), 2) Pulsed wave DTI of the mitral annulus (E'), thus allowing to obtain the ratio of mitral velocity to early diastolic velocity of the mitral annulus (E/E').
Results: The correlation between pre-A-wave pressure and E/E' was significant (r=0.60, p<0.01). In patients with LVEF >50% (n=20), no correlation was found (r=0.18, p=0.44), even when in patients with LVEF <50% (n=12), the correlation between pre-A-wave pressure and E/E' was very good (r=0.76, p<0.01). By ROC curve analysis, we identified an E/E' >9 to be the best cut-off value to fit with a pre-A-wave pressure >15 mmHg.



ROC curve.

Conclusion: In CAD-patients, DTI may allow to determine LV filling pressure >15 mmHg only for patients with LV ejection fraction <50%, with a E/E' cut-off value of 9.

327 Prognostic insights from combined pulmonary venous and mitral flow in acute myocardial infarction

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We have previously shown that the duration of pulmonary venous versus mitral flow velocity curves at atrial contraction provided an added value to the risk stratification of patients with left ventricular (LV) dysfunction. Recent data have shown that restrictive filling is associated with a poor outcome in patients with a recent acute myocardial infarction (AMI), but it is not known whether the assessment of the difference in duration of pulmonary venous flow (PVF) and mitral flow A waves can provide additional prognostic information.
To assess the prognostic value of the difference in duration of pulmonary venous and mitral flow at atrial contraction in patients with a recent AMI.
A Doppler echocardiographic examination was carried out in 148 patients (mean age 70±10 years) with a recent AMI (within two weeks) and LV ejection fraction <45% in sinus rhythm. Patients were categorized according to their mitral E wave deceleration time (EDT) and pulmonary venous flow (PVF) curves in: restrictive mitral flow pattern (characterized by an EDT <130 msec), 2) non-restrictive mitral flow pattern with the difference in pulmonary venous and mitral flow velocity duration at atrial contraction >30 msec, 3) non-restrictive mitral flow pattern with the difference in pulmonary venous and mitral flow velocity duration at atrial contraction <30 msec. All patients were subsequently followed-up for a mean period of 22±9 months.
During the follow-up, 38 patients died from cardiac causes and 29 were hospitalized for worsening heart failure. Multivariate Cox analysis revealed that PVF reversal exceeding in duration by >30 msec mitral atrial wave was the most important independent predictor of the combined end-point. Probabilities of survival free from cardiac events at Kaplan-Meier analysis were 75% in nonrestrictive patients with a <30 msec difference in duration of pulmonary venous and mitral atrial flow, 32% in nonrestrictive patients with a >30 msec difference in duration of pulmonary venous and mitral atrial flow and 22% in the restrictive group (p<0.0001 by Log-rank).
In patients with a recent AMI and LV dysfunction, an increased duration of pulmonary venous and mitral flow at atrial contraction can predict the prognosis for the combined end point of cardiac mortality and hospitalization for worsening heart failure. Patients with nonrestrictive filling and a greater difference in atrial wave durations had an intermediate event-free survival at follow-up with respect to the group with non-restrictive filling and a shorter difference in duration of the two waves and to the restrictive group.

328 Study of patients with coronary artery disease using the TEI – Tissue Doppler Imaging Index

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The TEI index has been used for the assessment of left ventricular (LV) function. The aim of this study was the evaluation of this index, based on a standard calculation, but also using TEI calculated from pulsed Tissue Doppler Imaging (TEI-TDI), in patients with coronary artery disease (CAD).

Methods: We studied 50 patients (mean age 60.9±9.8 years) with CAD and in sinus rhythm, compared with 15 healthy controls with similar age and sex distribution. All underwent SPECT thallium-201, coronary angiography (EF 42± 8.1) and a complete echocardiographic Doppler study. TEI was calculated using the equation TEI = ICT+IRT/ET, where ICT = isovolumic contraction time, IRT = isovolumic relaxation time and ET = ejection time. TEI-TDI was calculated in the same way after recording of tissue velocities in the left atrioventricular plane measured by pulsed TDI in the segments (septal, lateral, anterior, inferior, posterior) from the apical views. The mean TI-TDI was also calculated. Of the 50 patients, 33 (Group A) had segmental wall motion abnormalities (SWMA) and 19 (Group B) did not.

Results: The TEI did not differ significantly between CAD patients and controls (0.702±0.208 vs. 0.578±0.148, p = 0.079), but mean TEI-TDI was significantly greater in the former group (1.248±0.507 vs. 0.893±0.380, p = 0.04). Mean TEI-TDI differed significantly between Group A and controls but not between Group B and controls (1.454±0.514 vs. 0.893±0.388, p = 0.003 and 0.915±0.255 vs. 0.893 ± 0.388, p = 0.859, respectively). Mean TEI-TDI differed significantly between patients with only akinesia or dyskinesia and those with hypokinesia or without SWMA at the 5 sites of the left ventricle (1.648±0.413 vs. 1.148±0.482, p = 0.004). There was a significant correlation between mean TI-TDI and the wall motion score index (r=0.69). In Group B, the TEI-TDI of segments in the region of the left anterior descending (LAD) artery (anterior and septal) was significantly different from the control group ($p < 0.01$). In Group B patients a TEI-TDI > 1.2 had sensitivity 63% and specificity 76% for the detection of LAD artery disease, compared to 50% and 53%, respectively, for SPECT thallium-201.

Conclusions: 1) In CAD patients mean TEI-TDI seems to be better than TEI for the evaluation of LV function. 2) TEI-TDI is less useful a) in the presence of SWMA, depending on its severity; b) in the absence of SWMA, but when there is ischaemia in segments in the LAD region. 3) The precision of TEI- TDI in detecting LAD artery disease in patients without SWMA is at least comparable to that of SPECT thallium-201.

329 Myocardial regions supplied by stenosed coronary arteries have impaired resting diastolic function

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Background: It is recognised that areas of myocardium subtended by chronically stenosed coronary arteries have impaired diastolic properties with preserved systolic function. Tissue Doppler Echocardiography (TDE) allows us to regionalise abnormalities in an objective and non-invasive manner. Diastolic function, on both a global and regional scale, is impaired with increasing age.

Methods: 50 patients with angiographically documented coronary artery disease were aged and sex matched with normal volunteers. Pulsed wave TDE images were taken from the apex and systolic and early diastolic velocities measured at the septal (sep), lateral (lat) and inferior (inf) aspects of the mitral valve annulus and the free wall of the tricuspid valve annulus (RV). Direct comparison was then made between segments supplied by stenosed arteries (greater than 70% on angiography) and equivalent segments from the normal group.

Results: 147 myocardial segments were analysed per group. There was no significant difference in systolic velocities. Diastolic velocities are shown in the table. Diastolic abnormalities existed in myocardial territories supplied by stenosed coronary arteries when compared with both normally perfused myocardial segments from the same patient and also age-matched normal controls.

Regional early diastolic velocities

Age	Group	Inf	95% CI	Lat	95% CI	Sep	95% CI	RV	95% CI
40-49	Normal	12.3	11.7-12.9	13.2	12.5-13.9	9.5	9.0-9.9	12.0	11.2-12.7
40-49	Ischaemic	8.1**	6.5-9.7	9.8**	7.4-12.0	7.6*	6.0-9.2	7.8**	6.0-9.6
50-59	Normal	10.7	10.1-11.3	11.8	11.1-12.4	8.4	7.9-8.9	11.3	10.5-12.0
50-59	Ischaemic	7.6*	6.6-8.7	9.2*	7.7-10.7	6.9*	5.9-8.0	8.0*	6.9-9.1
60-69	Normal	9.1	8.3-9.8	10.3	9.4-11.1	7.3	6.7-7.9	10.7	9.7-11.6
60-69	Ischaemic	7.1*	6.4-7.8	8.6**	7.6-9.5	6.3	5.6-6.9	8.2*	7.5-9.0
>70	Normal	6.5	4.5-8.4	8.0	5.9-10.0	5.6	4.1-7.0	9.4	7.6-11.0
>70	Ischaemic	6.2	4.9-7.5	7.4	5.8-8.9	5.0	3.7-6.4	8.6	7.1-10.2

Velocities in cm/s. **p<0.01 *p<0.05

Conclusion: There is minimal overlap in early diastolic velocities in segments supplied by tightly stenosed coronary arteries and age-matched normally perfused areas in patients under 70. This technique shows promise as a non-invasive, non-stress tool for the investigation of possible coronary artery disease and now requires prospective evaluation.

EUROPEAN SOCIETY OF CARDIOLOGY LECTURE ON CLINICAL CARDIOLOGY

331 Aspirin improves not only the endothelium-dependent but also the β-adrenoceptor-related vasodilatation in patients with essential hypertension

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Patients with essential hypertension (eHYP) and hypercholesterolemia show an abnormal endothelium-dependent vasodilation which may be a risk factor for coronary heart disease. The benefit of treatment with acetylsalicylate (ASS) in prevention of coronary heart disease (CHD) is usually explained by inhibition of platelet-aggregation. It has been suggested in a preliminary report that ASS may improve endothelial dysfunction in patients with hypercholesterolemia. The mechanism may be related to an inhibition of synthesis/release of constrictive eicosanoid-metabolites.

Aim of our study is to examine the effect of ASS (500 mg) on endothelium-dependent and -independent regulation of vessel tone in patients with eHYP

Patients with eHYP as a single risk factor (n=24) (age 54.2 + 8.5 years, mean + SD) were included. Blood flow was measured in the forearm circulation by venous occlusion plethysmography during i.a. infusions of acetylcholine (15-40 μg/min), the β1/β2-non-selctive agonist orciprenaline (100-250 ng/min), and sodium-nitroprussid (1.6-3.2 μg/min). The measurements were repeated 15 minutes after an intravenous application of ASS-Lysin. The table summarizes the maximal increases in blood flow (D% of baseline,*p< 0.05 vs. before ASS).

	before ASS	after ASS
Acetylcholine max.	67.2 ± 26.3%	99.2 ± 27.2%*
Sodium-Nitroprussid max.	202.4 ± 31.5%	198.7 ± 30.1%
Orciprenaline max.	49.9 ± 17.9%	89.0 ± 15.8%*

Conclusion: ASS improved endothelial-dependent vasodilation in patients with eHYP. Furthermore, the β-adrenoceptor-mediated, but not the endothelium-independent vasodilatation using nitroprusside was improved. These results suggest that a cyclooxygenase-dependent, contractile co-factor may participate to NO- and β-adrenoceptor-signal-transduction pathway in eHYP patients.

332 Left ventricular functional characteristics in renovascular hypertension and in primary aldosteronism

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Objective A high prevalence of left ventricular hypertrophy (LVH) and concentric remodeling has been reported in patients with secondary forms of hypertension. Very few data are available on LV systolic and diastolic (Diast) performance in these patients. Aim of this study is to evaluate LV structural and functional characteristics in patients with renovascular hypertension (RVH) and primary aldosteronism (PA) in comparison with a control population.
Design and methods Eighty-two consecutive patients with secondary hypertension (30 RVH, 52 PA) and 196 age and sex matched, never treated, essential hypertensive controls (HT) were submitted to an echo-doppler study for evaluation of LV anatomy and function. LV mass index (LVMI) and relative wall thickness (RWT) were calculated; endocardial (end) and midwall fractional shortening (mid FS) were calculated to assess systolic performance. In addition transmitral E and A flow velocities, E wave deceleration time and isovolumic relaxation time were measured for diastolic filling evaluation.
Results are shown in the table:

	Controls	RVH	PA	ANOVA
BP mmHg	150(13)/93(8)	168(20)*/102(15)*	158(25)*/99(12)*	<0.001
RWT	0.38(0.08)	0.44(0.08)*	0.42(0.06)*	< 0.0001
LVMI g/m^2.7	45 (14)	56 (16)*	53(15)*	<0.001
LVH %	34	60*	58*	<0.05
FS end %	41 (8)	39 (7)	40(8)	ns
FS mid %	18 (3.5)	15 (2.7)*	16 (2.7)*	< 0.001
Dec E msec	151 (38)	149(91)	178 (55)*°	<0.005
Diast dysf %	28	37	45*	<0.05

* p < 0.05vs HT; ° vs RVH

All differences were confirmed after adjusting for clinic and 24hrs BP differences (ANCOVA).
Conclusion This is by far the largest study evaluating cardiac structure and function in RVH and PA, compared to age and sex matched never treated HT, indicating that neurohumoral factors may influence the development of structural and functional changes in the left ventricle.

333 Eight-year coronary risk in relation to baseline rule-of-halves blood pressure status: the Scottish heart health study

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Introduction A large cohort of men and women aged 40-59 sampled randomly from across Scotland were examined in 1984-87 in the Scottish Heart Health Study. Cross-sectional analysis showed that the population followed the "rule of halves" - half of hypertensives being undetected, half of those previously detected untreated, and half of those treated uncontrolled. Participants were followed for subsequent death, myocardial infarction and coronary artery surgery. We have examined eight-year coronary risk in relation to baseline blood pressure and rule-of-halves status.
Methods Subjects completed a questionnaire on medical history and medication. The mean of two random-zero sphygmomanometer readings was used to categorize their blood pressure. Risk factor levels including blood pressure were reported back to general practitioners. We have used the cut-point of ≥160/95 for hypertension and classified normotensives <120/80 as optimal, 120-129/80-84 normal, 130-139/85-89 high normal, and 140-159/90-94 high blood pressure. Hazard ratios were adjusted for age and multiple risk factors.
Results 5 754 men had 461 coronary events during follow-up, 5 875 women had 188 events. Compared to those with optimal blood pressure (RR=1.0) multiple adjusted RR with 95%CI in men were as follows: normal 1.43(0.95-2.16), high normal 1.66(1.12-2.47), high blood pressure 1.25(0.83-1.90),undetected 1.94(1.27-2.95),untreated 3.21(1.98-5.23),uncontrolled 3.22(1.97-5.29), controlled 2.58(1.61-4.15).
Equivalent adjusted RR with 95%CI in women (with fewer events)were:normal 0.94(0.49-1.83), high normal 1.55(0.86-2.81), high blood pressure 1.81(1.02-3.20),undetected 1.81(0.93-3.52),untreated 3.12(1.50-6.47),uncontrolled 2.63(1.24-5.57), controlled 2.69(1.39-5.23). These results included everyone at baseline - sub-group analysis excluding any evidence of coronary heart disease from symptoms, history or electrocardiogram at that time produced similar results.
Conclusions Findings from a single baseline survey clinic are very powerfully predictive of coronary risk over the next eight years. Rigorous attention is needed to detection, treatment and control of hypertension in the community along with management of accompanying risk factors. Our extended follow-up, now in progress, will show whether these risk differences have widened or narrowed during the later 1990s when newer drugs and attitudes to coronary risk factors were more prevalent.

ADDED VALUE OF STRESS ECHO IN PATIENTS WITH CHEST PAIN

334 Comparison of early dobutamine stress echo, exercise testing, and hospital admission in patients presenting to the emergency room with chest pain

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Management of pts presenting to Emergency Department (ED) with chest pain (CP) suggestive of acute coronary syndrome remains a continuing challenge, and these pts are often admitted to rule out acute myocardial infarction (AMI). To shorten in-hospital length-of -stay, maintain pt safety, and enhance cost-effectiveness, several startegies have been applied to the management of pts with CP. However, efficacy and safety of these strategies have never been compared in a randomized study.
To address this issue, a total of 290 pts (57% males, 54±11 years) with no ischemic EKG changes, negative serial CK-MB and cardiac troponin at 6 hours from ED presentation, and who were to be admitted, were enrolled in 10 participating centers and randomized to dobutamine stress echo (DSE, n= 109), or exercise test testing (ETT, n= 89), or hospital admission (H, n= 92). Eighty-seven (80%) pts were discharged after DSE, and 75 (84%) were discharged after ETT (p= NS). Pts with negative DSE or ETT were discharged with no or unchanged ischemic medications. All pts were followed for at least 2 month. The 3 pt groups were similar for age, gender distribution, clinical characteristics of CP and risk factors prevalence. No significant adverse event was observed during DSE or ETT. In pts in the H group there were 4 in-hospital events (4%): 3 AMIs, and 1 urgent coronary revascularization. Ischemic origin of the CP was diagnosed in 38% of the study pts. None of the pts discharged after DSE or ETT suffered a late major adverse cardiac event. During follow-up, 4 pts in the ETT group were readmitted to ED for CP, 25 pts underwent additional noninvasive diagnostic tests, and 2 underwent coronary angiography. Conversely, only 8 pts in the DSE group underwent additional noninvasive tests and there was no readmission (p<0.0001 vs ETT pts for both). In-hospital length-of-stay was 26±4 hours in the ETT pts, 26±8 hours in the DSE pts, and 72±11 hours in the H pts who were found not having an ischemic origin of CP (p<0.0001).
Thus, early DSE or ETT in ED pts with CP, normal serial biochemical markers of myocardial injury and EKG tracings at 6 hours from ED admission are safe and effective tools for early risk stratification. Accelerated diagnostic protocols incorporating DSE or ETT tests show an equivalent high negative predictive value for major adverse cardiac events during follow-up, and are less resource-consuming than usual hospital admission.

335 Stress echo in chest pain unit: the SPEED (Stress Pharmacological Echocardiography in Emergency Department) trial

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Background: emergency room (ER) evaluation of patients with acute chest pain and non diagnostic electrocardiography (ECG) remains a frequent and difficult problem. Aim: to assess the safety and prognostic implication of stress echocardiography in the ER chest pain unit (CPU).
Methods: 540 patients (326 males/age 58±12 years) with acute chest pain and negative serial cardiac markers, and ECG recordings and normal/unchanged resting left ventricular function, underwent stress echo (dipyridamole n= 520, dobutamine n=20) within 12-48 hours after admission. Six echo labs quality-controlled for stress echo reading entered the study. Follow-up was obtained in all patients after 12 ± 6 months.
Results: feasibility was 97%, no major side effects occurred during tests. Stress echocardiography was negative in 491 and positive in 49 patients. Patients with negative stress echocardiography were discharged with no or unchanged anti-ischemic medication. Patients with positive stress echo were admitted to coronary care unit. In 42 of them coronary angiography was performed and showed significant coronary artery disease in 40. There were 42 events in the follow-up: four (two acute myocardial infarction and two unstable angina requiring revascularization) in the 491 pts with negative and 38 (37 unstable angina requiring revascularization and one acute myocardial infarction) in the 49 patients with positive stress echo (0.81% vs 77.5%, p<.001). The negative predictive value of stress echocardiography for subsequent events was >99%.
Conclusion: Stress echocardiography is feasible, safe and effective tool for early stratification of patients with acute chest pain and non-diagnostic ECG, cardiac markers and resting echo admitted to the ER.

336 The incremental prognostic value of dobutamine stress echocardiography in chest pain unit patients with negative troponin levels

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Background: The prognostic value of elevated troponin (TnI) in acute coronary syndrome is well established. However, little is known about patients with chest pain but normal troponin (TnI) levels and their risk stratification with stress echocardiography in predicting future cardiac events.
Methods: We therefore prospectively studied 125 consecutive patients who were admitted with chest pain. Serial troponin determinations and echocardiographic images were prospectively evaluated. In 99 of the patients with negative troponin levels, stress echocardiography was performed. A positive event was defined as cardiac event (unstable angina, coronary artery revascularization, congestive heart failure or death) occurring during hospitalization or 3-month follow up.
Results:

The incremental prognostic value of dobutamine stress echocardiography in chest pain unit patients with negative troponin levels in predicting in hospital and short term cardiac events

	Positive Predictive Value	Negative Predictive Value
Troponin	75%	81%
Troponin and Stress Test	69%	98%
Fisher's Exact:	P=NS	P=0.01

Conclusion: Stress echocardiography increased significantly the negative predictive valve of patients with normal troponin. Stress echocardiography adds incremental prognostic information in predicting future cardiac events in low risk patient population. In addition, combination of stress echocardiogram result with negative troponin levels allows 98% confidence level when discharging the patient for three month follow up.

337 Ischaemia-induced interleukin-6 and tissue factor are related to persistent left ventricular dysfunction after dobutamine stress echocardiography

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Interleukin 6 (IL6) and macrophage colony stimulating factor (MCSF) plasma levels are elevated after acute myocardial infarction. IL6 has an inherent negative inotropic action and mediates the ischemia-reperfusion myocardial injury. We investigated whether ischemia induces cytokine production leading to a) increased tissue factor (TF) expression and b) persistence of regional wall motion abnormalities (RWMA) during recovery after dobutamine stress echocardiography (DSE) in patients with stable angina(SA).
Methods: 80 patients with SA were studied by DSE. Blood samples were obtained at rest, at peak stress and 20min after cessation of dobutamine infusion (rec) for measurement (median, 25th-75th percentile) of MCSF, IL6 and TF plasma levels (pg/ml). Patients had angiograpically documented CAD. New or worsening RWMA at peak stress and their duration in the rec were noted.
Results: Forty five patients presented ischemia during DSE. Patients with and without ischemia achieved similar heart-rate product at peak stress. IL6 and TF levels increased at peak stress and at rec compared to rest in ischemic but not in non-ischemic patients (Table, $p<0.05$). MCSF levels were similar at rest, at peak stress and rec in all patients. The time to recovery of RWMA was related with IL-6 plasma levels at peak stress and rec ($r=0.51$ and $r=0.39$ $p<0.05$). Patients with RWMA lasting>5 min in rec (n=20) had higher IL6 at peak stress and rec than those with RWMA lasting <5 min (peak stress: 3.3 (2.4-4.6) vs 2.0 (1.5-2.7), rec: 2.7 (2.3-4.3) vs 1.9 (1.4-2.7), $p<0.01$). High MCSF was related with high TF only in ischemic patients in rec ($r=0.61$, $p<0.01$).

DSE	IL-6			TF		
Patients(n=80)	Rest	Stress	Rec	Rest	Stress	Rec
Ischemic* (n=45)	2.1 (1.5-2.8)	2.5 (1.7-3.3)	2.4 (1.6-3.4)	266 (132-405)	310 (243-553)	385 (141-577)
Non-ischemic (n=35)	2.1 (1.3-3.2)	2.1 (1.4-3.5)	2.2 (1.4-3.6)	371 (142-576)	312 (210-590)	328 (265-600)

*$p<0.01$ stress and recovery vs rest in ischemic patients

Conclusion: Reversible ischemia induces an increase of IL-6 and TF plasma levels that is sustained in recovery after DSE. MSCF is related to TF plasma levels during the post ischemic period. Ischemia-induced increase of IL6 persisting throughout recovery may explain the persistent left ventricular dysfunction observed in the post-ischemic period after DSE since this cytokine has an inherent negative inotropic action.

338 Dobutamine-stressechocardiography: means to reduce investigation time to detect ischaemia

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Aim: Dobutamine- stressechocardiography (DSE) is a well accepted but time-consuming test to define myocardial ischemia. The purpose of the study was to evaluate means to reduce investigation time to document myocardial ischemia.
Patients and methods: DSE wer performed in 102 patients (pat) for localizing or proving ischemia with a standardized protocol (group A: stepwise increase of dobutamine-infusion with 5,10,20,30,40 gamma/kg/min with addition of atropine if necessary to reach submaximal heart rate). For comparison we performed DSE in 100 pat with adding physical exercise (handgrip, leg elevation) to the same protocol (group B) and DSE in another 62 pat with constant infusion of 50 gamma dobutamine/kg/min during the whole test together with handgrip (group C). Pat were 60±11 years old (187 male/ 77 female), had a bodymass-index (BMI) of 27kg/m^2, were on betablockade in 53% and had myocardial scars in 33%. None of the investigation was terminated due to side effects.
Results: 41% of pat had an ischemic response (50% of those with and 39% of those without chest pain in pat history). Groups did not differ in age, sex, BMI, use of betablockers, maximal ST-segment depression, localisation and existing ischemia, scars, resting and maximal heart rate, ejection fraction and enddiastolic volume. However maximal double-product was higher and use of atropine was lower in group C than in group A ($p<0.03$). Duration of the test (stimulation and recovery time without time to prepare the test or interpretation) in group A/B/C were 1026±192, 919±204 and 654±216sec ($p<0.006$) with a mean difference of -107sec between A/B and -265sec between B/C. Total reduction for the stimulation time for high-dose dobutamine/ handgrip to standard protocol was -30% for pat with and -49% for pat without betablockade without difference in provoked arrythmias ($p<0.0001$).
Conclusions: Adding simple dynamic stress with handgrip and changing from a standard stepwise increase DSE to a constant high-dose DSE with 50gamma dobutamine- infusion has the potential to reduce atropine-dosage significantly and total stress/recovery time of 36% without provoking more side effects, although producing even higher pressure-heart-rate-double product. This simple change of protocol could be of importance for DSE in clinical practice.

339 Comparison of peak and postexercise treadmill echocardiography for the detection of multivessel coronary artery disease

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Objectives: We sought to compare the feasibility and accuracy of peak (Pk) treadmill exercise echocardiography (EE) versus postexercise echocardiography (PE) for identification of multivessel (MV) coronary artery disease (CAD) and to assess its incremental value when combined with clinical and exercise test variables.
Background: Although peak exercise echocardiography has been reported for both bicycle and treadmill exercise and has shown higher sensitivity than postexercise imaging, little is known about its utility for identifying multivessel CAD.
Methods: The study group included 335 patients (228 men; mean (±SD) age 60±11). Two hundred seventy nine patients were included on the basis of having had an EE between 1998 and 2000 and a coronary angiography (CA) within 4 months of the EE. To avoid bias to CA a subgroup of 56 consecutive non-diabetic patients referred for EE with pretest probability of CAD <10% that had atypical chest pain or were asymptomatics were also included. These latter patients were considered as having no CAD. MV CAD (> 49% diameter stenosis in >1 coronary artery, major branch, or by-pass graft) was confirmed in 170 patients, whereas 165 patients were considered to have 1-vessel CAD or no CAD. Positive EE was defined as ischemia or necrosis in at least 2 coronary territories.
Results: PE images were acquired within 125 seconds after exercise (49±15). Mean heart rate (bpm) was 139±19 at Pk versus 117±22 at PE ($p<.001$). Interpretable Pk and PE images were obtained for all patients. Sensitivity for detecting MV disease was higher with Pk than with PE imaging (79% vs. 55%, $p < 0.001$), with lower specificity (79% vs. 88%, $p< 0.05$). Predictive positive value was similar (80% vs. 83%). Negative predictive value was again higher with peak imaging (78% vs. 66%, $p< 0.01$). Total accuracy was not different (79% vs. 72%). A stepwise logistic regression analysis identified Pk EE positivity for MV CAD as the strongest independent predictor of MV disease (OR: 7.36); also significant were male gender (OR: 4.22), diabetes mellitus (OR: 4.28), previous myocardial infarction (OR: 3.12) and increment of product heart rate x blood pressure (OR: 1.00).
Conclusions: Pk treadmill EE is technically feasible and has higher sensitivity and negative predictive value for MV disease than PE echocardiography. This method adds independent and incremental value to clinical and exercise variables for the diagnosis of MV CAD. Therefore in the clinical setting Pk EE should be performed to diagnose MV CAD.

COMPUTER DEMONSTRATION

345 Computerized simulator for study of coronary artery physiology

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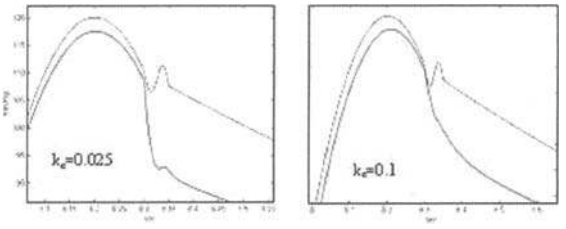
Introduction: Recognized shortcomings in angiographic imaging, has led to increasing interest in the assessment of real time physiology in the catheterization laboratory. Among the parameters currently being used clinically are CFR, FFR, rCFR, Pulse Transmission Coefficient (PTC), and Collateral Flow Index (CFI). Interrelationships between these parameters yield information that can be lesion and/or vascular bed specific. To better understand the interrelationships between varying hemodynamic parameters we have created a computer model of the coronary circulation.
Methods: The simple hydraulic model of coronary stenosis is used together with the windkessel model of the vascular bed. The compliance of the vascular bed is assumed to be inverse to its resistance. The systolic/diastolic change in resistance is described by step-wise functions of time. Input parameters are: aortic pressure signal, number of stenosis, length of each stenosis, MLD of each stenosis, reference diameter, rCFR, systolic/diastolic velocity ratio, CFI, and a constant Kc representing the ratio of vascular bed compliance to vascular bed resistance. The output of the model is coronary flow and the pressure signal distal to each stenosis at rest and at hyperemia.
Results: Fig 1 illustrates the simulated effect of changes in vascular bed compliance on the shape of distal pressure waves. Comparable analysis on the interrelationships of reference CFR, collateral flows and multiple lesions on CFR and FFR will also be demonstrated.



Conclusion: The demonstrated computer model allows for the estimation of the physiologic changes. It can be used for the design of clinical and animal studies. It is also valuable for demonstrating the usefulness of physiologic study to interventionists.

346 Psychological distress versus quality of life in chronic heart failure: validation of a new dedicated software

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Quality of life (QOL) of patients (pts) with chronic heart failure (CHF) is associated with severe reduction in functional capacity (FC), limitations in social life (SL), alterations of the emotional (E) status and therapy compliance (TC). All such conditions are generally accompanied by a deep state of psychological distress. An objective measure of all such conditions is however still undefined. The alterations in FC, SL, E and TC of 69 pts with CHF were then calculated with a score from an interview consisting in 32 graded questions on QOL. The same method was carried out in other 50 pts but without CHF (control group). The alterations in FC, SL, E and TC were then expressed as percentage reduction from the values observed in control pts.
All pts were invited to self-rating in a visual graded scale (0 = normal, 100 = maximal values) their psychological distress burden. The amount of psychological distress was also evaluated by a pt close relative by using the same method. A modified Maastricht Questionnaire, self-ratings and ratings by a close relative was also submitted to all pts. Major determinants of psychological distress were assessed by the Life Events Assessment, the Social Support Questionnaire and the Ways of Coping Checklist. Browsing on the computer screen, the software provides informations on the clinical status of the 69 pts under study: mean age of 69±11 years,37±12% mean ejection fraction (EF) on echocardiography, 3±1 mean New York Heart Association (NYHA) class. This software also automatically illustrates with graphics that, in pts under study, the percentage reduction in FC, SL,E and TC was of 61±13%, 46±15%, 36±32%and 23±17%, respectively. The self and relatives ratings of psycological distress showed, on an other separate graphic, a percentage increase of 58±27% and 54±29%, respectively. These values were significantly correlated (Pearson r> 4,P < 0.001) with the Modified Maastricht Questionnaire results. These data indicate that a high level of psychological distress is detectable in pts with CHF and that it parallels the reduction of QOL. The use of this validated software is rapid (it takes less than 10 min to complete it) and objective and it may facilitate counseling and treatment in pts with CHF.

POSTER DISPLAY I

MODERATED POSTER SESSION I

P347 Absence of correlation between stress SPECT imaging and angiography at 6 months after direct angioplasty for acute myocardial infarction

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Background: Restenosis of the infarct-related artery after direct angioplasty (d-PTCA) for acute myocardial infarction (AMI) is often silent. The value of stress SPECT imaging performed systematically at 6 months-follow-up (FU) for detecting myocardial ischemia due to restenosis in asymptomatic patients (pts) who underwent d-PTCA with stenting (d-S-PTCA) for AMI has not been well evaluated.
Methods: Among a cohort of 440 consecutive AMI pts successfully treated by d-S-PTCA for AMI in our institution from 01/99 to 08/01, 75 pts with no symptom during the F-U systematically underwent both rest thallium 201/stress Tc-99m setamibi myocardial perfusion (SPECT) and coronary angiogram (CA) at 6 months.
Results: Binary angiographic restenosis rate was 32%. Reversible ischemia at SPECT in the territory of the infarct related artery was observed in 34 of the 75 patients (45%); among these 34 patients with positive SPECT, only 10 had angiographic restenosis. Among the 41 patients without reversible ischemia at SPECT, 14 had restenosis. Specificity, sensitivity and positive predictive value of SPECT for detecting restenosis were 32%, 53% and 30%, respectively. Patients with SPECT reversible ischemia at 6 months-FU did not differ from those without SPECT reversible ischemia regarding restenosis, initial angiographic LVEF, diabetes, hypertension, exercise peak workload. Patients with SPECT reversible ischemia had a higher LV ejection fraction at 6 months than those without reversible ischemia (67±8% vs 61±13%, p=0.03).
Conclusion: These data suggest a poor correlation between stress SPECT imaging and angiographic restenosis at 6 months in patients treated by direct angioplasty for AMI and who remain asymptomatic at follow-up. These findings should be taken into account in the strategy of the clinical follow-up of this population.

P348 Relationship between electrocardiogram and electrophysiological findings and the extension of DNA mutation in patients with Steinert myotonic dystrophy

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Background: Myotonic dystrophy (MD) is the most frequent autosomal dominant muscular dystrophy in adult life. MD is caused by an amplified and unstable trinucleotide cytosine-thymine-guanine (CTG) repeat on chromosome 19. Cardiac conduction disorders and arrhythmias are common in MD, but a correlation between length of CTG expansion and severity of cardiac involvement is debated.
Methods: In order to assess whether CTG repeat length is correlated to cardiac involvement, we studied 90 pts (age 43±15 years, 49 women) with a genetic diagnosis of MD. All pts underwent 12-lead ECG and 24-hour ECG Holter monitoring (HM). 21 pts with an AHA class 1 or 2 indication underwent also electrophysiological study (EP).
Results: The number of CTG repeats was positively correlated to heart rate (HR), (r= 0.29, p= 0.032) and inversely correlated to QT (r=-0.34, p=0.012) and QTc (r=-0.33, p=0.014) intervals. In contrast, CTG repeats were not correlated with P-R interval and their number was not different in patients with (n=21, 810.1±513.0) or without (n=69, 743.6±440.2) intraventricular conduction defects (p=0.57). HM data revealed that CTG number was similar in patients with (n=8, 918.7±511) or without (n=82, 876±456) ventricular pauses (p=0.42) but tended to be significantly increased in those with (n=9, 1059.3±572.6) compared to those without (n=81, 751.9±434.0) frequent and/or repetitive ventricular arrhythmias (VA), (p=0.056). Finally, among pts who underwent EP, CTG number was not significantly different in those who developed (n=8) and in those who did not develop (n=13) sustained VA (1093.2±431.9 vs. 769.8±462.7; p= 0.24).
Conclusions: CTG repeat length in MD pts is (1) positively correlated with with HR and spontaneous VA (2) inversely correlated with QT/QTc intervals (3) is not correlated with impairment of cardiac conduction and to inducibility of sustained ventricular arrhythmias. Mechanisms underlying these correlations need to be clarified to discriminate whether our observation are explained by a primary alteration of cardiac function caused by CTG repeat lenght in cardiomyocytes or merely represent the cardiac effects of neurohormonal changes caused by extracardiac manifestations of MD.

P349 Determination of the accessory pathway location by the QRS polarity in the electrocardiogram of children with Wolff Parkinson White's syndrome

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Introduction: The QRS polarity (QRSP) in the ECG has been used to predict the accessory pathway (AP) location in adults with WPW syndrome. In children this may fail due to electro-anatomic differences and we therefore sought to verify or improve the existing algorithm.
Methods: The ECGs of 173 symptomatic children with WPW syndrome were collected, blinded, and evaluated by 2 experienced electrophysiologists. The QRSP was designated as mainly positive (+), intermediate(=), or negative (-) for the 12 individual ECG leads. A previously validated algorithm for adults (d'Avila, PACE 1995) was used to predict the AP location by the QRSP pattern in leads V1, III, aVL, II, and V2. The AP location had been established fluoroscopically during electrophysiological study and radiofrequency ablation. The AP locations were designated as LL, LPS, PS, RPS, RL, AS, MS, or Parahisian (PH).
Results: The ECGs of 157 patients with sufficient pre-excitation were included in the study. The age of the children was 13±3 yrs, 55 were female and 102 were male. With the existing QRSP algorithm for adults, the 2 observers predicted only 55% to 58% of AP locations correctly and a new algorithm had to be devised. Based on a + or = QRSP in V1 as a first step, the 61 left sided APs were all detected but an additional 10 ECGs were of PS, MS, or RPS APs. The 47 LL APs could all be distinguished by a + QRSP in III and a - or = QRSP in I. The 18 LPS and PS APs had a - or = QRSP in III but could not be further separated from the 6 MS and RPS APs. For ECGs with a - QRSP in V1 the existing adult algorithm using leads III, II, and V2 failed significantly. Instead, the introduction of a + QRSP in V3 and + or = QRSP in aVF was found to differentiate most PH (7 of 12) and AS (4 of 8) from most RPS (21 of 26) and MS (8 of 13) APs that showed a + QRSP in V3 but a - or = QRSP in aVF. The majority of RL (25 of 31) but also some AS (4 of 8) an PH (4 of 12)AP were characterized by a - or = QRSP in V3. Especially the AS, but also MS and Parahisian AP, showed heterogeneous ECG patterns and were difficult to classify. The use of additional ECG leads provided no contribution for further classification. There did not seem to be a clear relationship between age and electrocardiographic expression of APs.
Conclusions: In children with WPW the ECG manifestation of the AP is more heterogeneous than in adults. AS and Parahisian AP are most difficult to diagnose. The new QRSP algorithm based on leads III, aVF, V1 and V3 has a 90% overall reliability to predict the AP location in five regions of the heart.

P350 Internal cardioversion of atrial fibrillation: which role in the era of external biphasic shock?

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Background: Internal cardioversion (IC) of atrial fibrillation (AF) has been indicated for converting atrial arrhythmias mainly refractory to external cardioversion (EC) delivering monophasic shock (MS).
Aim of the present study was to evaluate the role of IC in the era of external biphasic shock (BS)
Methods: The study population consisted in 135 patients (pts), mean aged 69±8 years, with their first episode of AF lasting 3 days to 12 months (mean arrhyhmia duration 150±97 days), NYHA functional class I-II, who received anticoagulation 3 weeks before and 4 weeks after external cardioversion. Pts received MS-EC using a step-up protocol (3 J/Kg anterior-posterior (AP), 4 J/Kg AP, 4 J/Kg anterior-lateral (AL), maximum 360 joules), if arhhythmia persisted a BS-AP-EC at the maximun energy previously delivered was administrated. Pts still refractory to BS-EC underwent IC. No additional antiarrhythmic drugs were given. End-point of the study was resumption of sinus rhythm (SR).
Results: Sixteen (12%) pts were excluded because of spontanous reversion to SR before EC. The main results are reported in the table.

Efficacy	3 J/Kg MS-AP	4 J/Kg MS-AP	4 J/Kg MS-AL	4 J/Kg BS-AP	IC
Pro-step	57/119 (47,9%)	26/62 (41,9%)	18/36 (50%)	17/18 (94,4%)	1/1 (100%)
Total	57/119 (48%)	83/119 (70%)	101/119 (85%)	118/119 (99%)	119/119 (100%)

Arrhythmia duration predicts only MS-EC failure (182±86 days in non-responder vs 132±94 in responder pts; p=0.038).
Conclusions: The use of biphasic shock for external cardioversion rises the success rate of the procedure very close to 100%. The need for internal cardioversion in patients with their first episode of atrial fibrillation lasting < 1 year, is less than 1%, therefore the use of the invasive procedure in this clinical setting must be very limited.

P351 Thromboembolic complications after direct current cardioversion in patients with atrial fibrillation and ineffective anticoagulation

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The Ludwigshafen atrial fibrillation (AF) study is a prospective single center observatinal study on an intention to cardiovert basis, including 1269 consecutive unselected patients (pts) with AF. Aim of the substudy was to evaluate the embolic event rate in pts with AF and ineffective anticoagulation (IA), in whom electrical cardioversion (CV) was intended. IA was defined, if warfarin was given, however INR was < 2, or if no anticoagulation was performed. Reasons for performing CV in pts with IA were AF of < 48 h, hemodynamic instable AF, or contraindication for anticoagulation. After cardioversion an overlap of warfarin therapy and intravenous heparin was given to maintain adequate anticoagulation after CV in pts without contraindications for anticoagulation.
Results: In 193 pts (15%) anticoagulation therapy was ineffective at the time of the intended CV. Transesophageal echocardiography (TEE) was performed in 126 pts, in the remaining 67 pts transthoracic echo was performed. A thrombus was found in 10 pts (7.9%) of the 126 pts with AF and ineffective anticoagulation. In 53 of the 126 pts (42%) TEE revealed spontaneous echo contrast. The grade of spontaneous echo contrast was mild in 74%, moderate in 19% and severe in 9%. In 150 of the 196 pts (78%) CV was performed, in the remaining 43 pts no CV was performed. In 2 of 150 pts (1.3%) with AF and IA a transient ischemic attack occurred in the first 4 weeks after CV. In both pts TEE was performed before CV, none of the pts had evidence of left atrial thrombus. In none of the 43 pts without CV a thromboembolic complication occurred. In comparison the rate of thromboembolic complications in the first 4 weeks after CV was 0.8% (9/1076 pts) in pts with AF and effective anticoagulation at least 3 weeks prior to CV.
Conclusion: 1) In our AF outpatient clinic 15% of the pts with AF had ineffective anticoagulation prior to CV. 2) The rate of embolic events in first 4 weeks after the intended CV was 1.3 in pts with ineffective anticoagulation compared to 0.8 in pts with effective anticoagulation.

P352 Influence of reciprocating tachycardia on development of atrial cardiomyopathy in WPW patients

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Background Stretch of cardiac tissues resulting from pressure-overload is a confirmed trigger for atrial fibrillation (AF). Atrial strech during atrio-ventricular reentry tachycardia (AVRT) is suspected source of AF in WPW patients
Objective was to evaluate influence of AVRT on atrial pressures during tachycardia and presence of AF in WPW syndrome
Methods Study population consisted of 88 consecutive patients with left-sided accessory pathway (AP) and stimulated AVRT during electrophysiologic study (EPS). Studied group (Gr-I, n=32, 36.36%) consisted of patients with sustained episodes of AF during EPS, control group (Gr-II, n=56, 63.64%) PTS without AF. Mean and maximal pressure during AVRT in both atria were evaluated using transseptal approach (LAP mean, LAP max, RAP mean, RAP max). Relation between atrial pressures and electrophysiological parameters of AVRT: A-V, V-A conduction time, indexes A-V/V-V, V-A/V-V were calculated in the entire population
Results We found significantly higher values of atrial pressures in Gr-I compared with Gr-II: LAP max 32.0 mm Hg versus 20.8, LAP mean 21.6 versus 13.2, RAP max 15.2 versus 11.5, RAP mean 8.2 versus 6.17 respectively ($p<0.001$). Analysis of the influence of AVRT on atrial pressures showed significant ($p<0.001$) negative correlation between A-V-conduction times, A-V/V-V indexes and LAP max, LAP mean and positive($p<0.05$) correlation between V-A conduction times, V-A/V-V-indexes and LAP max LAP mean. Similar effect of AVRT was found analyzing right atrial pressures.The most significant correlations were found between LAP max and A-V conduction time (r=-0.64), A-V/V-V, V-A/V-V indexes (r=-0.60, r=0.60 respectively).

	LAPmax	LAPmean	RAPmax	RAPmean
A-V	r=-0.64	r=-0.57	r=-0.25	r=-0.26
V-A	r=0.36	r=0.32	r=0.23	r=0.11
A-V/V-V	r=-0.60	r=-0.54	r=-0.30	r=-0.20
V-A/V-V	r=0.60	r=0.54	r=0.30	r=0.20

Conclusions 1.Electrophysiological parameters of AVRT have an influence on atrial pressures and presence of AF in WPW patients.
2.Earlier ventricle and later atrial activation during AVRT increase atrial pressures.

P353 Electrophysiological effects of novel Kv1.5 channel blockers on left versus right pig atrium in comparison with IKr-blockade

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Objectives: Inhibition of the cardiac Kv1.5-channel, the molecular base for the human cardiac ultrarapid delayed rectifier potassium current (IKur), is considered a new promising atrial selective antiarrhythmic concept since this channel is presumed to contribute to atrial but not ventricular repolarization in the human heart. In a previous study in pigs we found clear baseline differences in refractoriness between left and right atrium with shorter effective refractory periods (ERP) of the left atrium associated with a high vulnerability for tachyarrhythmias of the left, not the right atrium. In this newly established model we compared atrial and ventricular effects of three novel Kv1.5-blockers, S9947, S20951 and S1185, with the IKr-blockers dofetilide, azimilide, ibutilide and d,l-sotalol.
Methods: In pentobarbital anesthetized pigs (n=40) we determined ERPs in the free walls of both atria with the S1-S2-stimulus method at three basic cycle lengths (BCL 240/300/400ms)and the QTc-intervals. The incidence of atrial tachyarrhythmias triggered by the S2-extrastimulus of the left atrium was evaluated (left atrial vulnerability).
Results: In contrast to IKr-blockade, Kv1-5-blockade had no effect on the QTc-interval, but prolonged the atrial ERP. The Kv1.5-blockers were significantly stronger on left atrial ERP, Ikr-blockers on right atrial ERP ($p<0.05$ for all compounds tested). A 240 ms BCL the Kv1.5-blocker S9947,1mg/kg, prolonged left vs. right atrial ERP by 20±2% vs. 12±3%; S20951, 3mg/kg, by 29±7% vs. 9±2% and S1185, 1mg/kg, by 54±7% vs. 23±7%. By contrast the effect of dofetilide,10μg/kg, was stronger on the right than left atrium (36±4% vs. 23±2%), a profile also found with azimilide (5mg/kg, 33±2% vs. 17±3, ibutilide (15μg/kg, 40±9% vs. 23±5%) and d,l-sotalol (1.5mg/kg, 41±5% vs. 30±4%). The Kv1.5-blockers, S9947, S20951 and S1185, significantly decreased left atrial vulnerability (-62, -75 and -100%, respectively, $p<0.01$) in contrast to the selective IKr-blocker dofetilide(-14%, n.s.).
Conclusion: Kv1.5- and IKr-blockers showed substantial differences in their atrial and ventricular actions in pigs. IKr-blockers were stronger on right atrial ERP, Kv1.5-blokckers on left atrial ERP suggesting interatrial differences in the expression of potassium channels. In contrast to selective IKr-blockade, Kv1.5-blockade inhibited left atrial vulnerability and had no effect on the QT-interval. Based on the atrial selective prolongation of refractoriness and the inhibition of left atrial vulnerability Kv1.5 channel blockade seems a promising atrial antiarrhythmic concept.

P354 Topographic location of the human sinus node: implications in radiofrequency catheter ablation of inappropriate sinus node tachycardia

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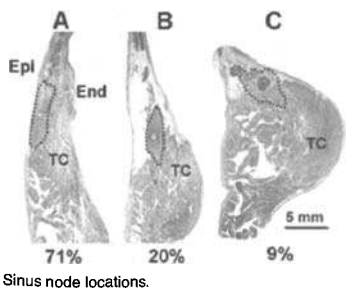
Treatment of inappropriate sinus tachycardia with radiofrequency (RF) catheter ablation has lower success rates than those attained in other atrial tachycardias. No systematic investigation has been made on the anatomic relations of the sinus node (SN) and the endocardial and epicardial aspects of the right atrium (RA), and the terminal crest (TC) in the human heart.
Methods: In 45 autopsied normal human heart specimens (49±20 years; 31 male), we examined by longitudinal sections the location of the SN body within the TC and the distance to the RA epicardium and endocardium.
Results: The SN body, constantly formed around a central sinus node artery, had a variable shape structure, which extended along the TC in lateral position, gradually passing through the middle of the crest to reach the endocardium at variable distances. Its location in relation to the RA epicardium and endocardium could be assigned to 3 different patterns (figure). In 32 specimens (71%) the SN was subepicardial at the junction of the superior caval vein and the RA (type A). The distance SN-epicardium was 0.5±0.2 mm and SN-endocardium 4.0±0.4 mm. In 9 hearts (20%) the SN was located in the middle between the epicardium (epi) and endocardium (end) (type B). In 4 specimens (9%) the SN was subendocardial and the distance SN-endocardium was 0.8±0.3 mm (type C).
Conclusions: In 71% normal human hearts the SN body has a subepicardial location. This combined with the presence of a central sinus artery and a thick muscular TC between the SN tissue and the RA endocardium probably accounts for the difficulties in ablating with RF inappropriate sinus tachycardia.



Sinus node locations.

P355 Left atrial macroreentry tachycardia after mitral valve surgery: complete conduction block across the critical isthmuses can prevent recurrence

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The reentry circuit of left atrial macroreentry tachycardias (LAMRT) after mitral valve (MV) surgery are complex and data about results of RF ablation are limited. We investigated 9 pts. (3 f; age 18-70 y) with LAMRT after MV surgery with CARTO. Mapping in LAMRT was possible in 7 pts. In 2 pts we performed substrate mapping in sinus rhythm. Ablation endpoint was complete conduction block across all identified critical isthmuses CIs and non-inducibility.
Results: In addition to an electrical silent area (ESA) or line of double potentials (LDP) anterior of the right pulmonary veins (PV) representing the atriotomy in 8/9 pts acquired electrical barriers were identified. 17 tachycardias were mapped in 7 pts (1-3/pt, CL 250 - 440 ms). In 12/17 dual loop mechanism was suspected with the CI between a posterior ESA/LDP and a PV (6), between 2 posterior ESAs (3) or a posterior ESA and the atriotomy (3). An additional 5 were single loops around the mitral annulus (3 counter-clockwise, 2 clockwise) with isthmus at the lateral (3) or anterior (2) mitral annulus (MA). Finally all CIs could be blocked by delivering 4.0±0.8 RF pulses at sites with a maximal bipolar amplitude of 0.08 - 3.24 mV. 2 CIs located between the lateral MA and a posterior ESA with amplitudes of 3.24 and 1.89 mV and a widths of 26.6 and 31.4 mm (average widths of all CIs: 14.0 ± 8.8 mm) required cooled ablation after recurrence.
During a follow up of 14 ± 9 mon no LAMRT occurred. 7/9 pts were completely arrhythmia free, 2 were symptomatic with intermittent AF.
Conclusion: Electroanatomical mapping in LAMRT pts after mitral valve surgery reveals ESAs or LDPs due to atriotomy, additional ESAs, and allows identification of the critical isthmus and mechanism of tachycardia. Complete conduction block across the critical isthmuses prevents recurrence of LAMRT.

P356 The post-pulse sodium spike as a marker of cardiac capture: from modelling to clinical evidence

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Introduction: A pacemaker assuring myocardial capture, through automatic output adjustments, would improve patient safety, extent battery life and speedup follow-ups. At the upstroke of action potential the impedance of cell membrane strongly decreases due to the opening of sodium channels (NaCh). During this phase lasting 2-4 ms, myocardial impedance decreases accordingly. Theoretical models of membrane kinetics show that a short living negative dip in intracardiac impedance is expected soon after a captured pacing pulse (within 20 ms).
Aim of this preliminary clinical investigation was to verify whether right ventricular capture can be recognized from intracardiac impedance changes resulting from NaCh opening.
Material and methods: Six patients implanted with an Inos2 CLS pacemaker (Biotronik, Germany)and low-polarization leads, were paced in DDD mode at pulse amplitudes below and above the threshold value. The bipolar intracardiac impedance was DC measured in right ventricle by the pacemaker and downloaded via telemetry in a laptop PC for post-processing.
Results: In all pts, a small (mean 2.9 ± 0.8 Ohms) and fast (< 6ms) intracardiac impedance dip could be detected 10-18 ms after the ventricular capture. This dip was not observed after non-captured events. The mean DC intracardiac impedance was 542 ± 50 Ohms.
In conclusion, an ultra-fast (within 20 ms) detection of capture is feasible by an impedance-based method. Since impedance measurement is slightly affected by polarization artifacts, such method is expected to work with any lead.

LONG-TERM BIVENTRICULAR PACING RESULTS

P357 Effects of biventricular pacing on morbidity and mortality in patients affected with severe congestive heart failure

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Biventricular pacing is a new treatment for severe congestive heart failure that has proven to be effective in several studies.
Since October 1998 to December 2001, we have implanted 82 patients with a biventricular device. 54 patients have until today at least 1 year of follow-up. 6 died during the first year after the implant, so that the mortality rate at 1 year is 11.1%. 3 patients died for sudden cardiac death, 2 for congestive heart failure and 1 for non cardiac death.
For the morbidity analysis, we have studied in the year before and in the year after implant: days to first recurrence of CHF, number of acute episode of CHF, number of hospitalisation in the Cardiology Division and in the ICU, length of hospital stay in the Cardiology Division and in the ICU.
The table shows the results, expressed ase mean±1 standard deviation.

Morbidity parameters

	DFR	NAC	NHC	NHI	LHSC	LHSI
1 year pre	124+134	2.8+1.4	2.6+1.5	0.7+1.0	36.5+31.7	1.9+2.9
1 year post	298+108	0.4+0.7	0.5+1.4	0.06+0.24	4.4+12.3	0.08+0.35

DFR = Days to first recurrence, NAC = Number of acute episode of CHF, NHC = Number of hospitalisation in Cardiology Dept., NHI= Number of hospitalisation in ICU, LHSC=Length of stay in Cardiology Dept, LHSI = Length of stay in ICU

All differences are statistically significant.
If the particular severity of our patients is considered (mean NYHA class 3.1±0.3, mean ejection fraction 22±7%)our results on mortality are satisfying. Furthermore, our data demonstrate that biventricular pacing not only is hemodinamically and clinically efficacious, but it is also related to a significant decrease in morbidity rate.

P358 Long-term benefit in quality of life by biventricular pacing in patients with chronic heart failure and atrial fibrillation in the MUSTIC study

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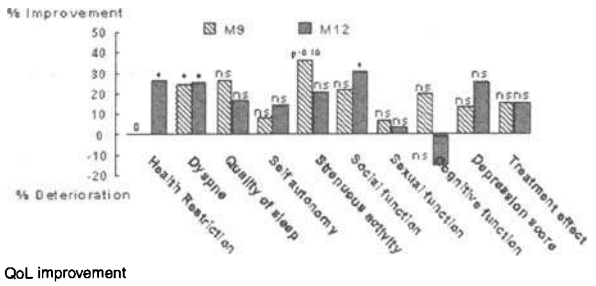
The MUltisite STimulation In Cardiomyopathy (MUSTIC) study is a controlled multicentre trial, to assess the clinical efficacy of biventricular pacing (BIV) in patients with chronic NYHA III heart failure and intrinsic QRS>150 or RV paced QRS>200 ms. We have reported symptomatic relief from the crossover phase (CO) with sustained results over one year. The aim of this study was to assess quality of life (QoL) over time in the group of patients with atrial fibrillation (AF) and slow ventricular rate either due to spontaneous rhythm or His-ablation.
Methods: The 6 month CO single blind comparison of BIV and no-BIV was completed in 41 of 64 included. Of these, 35 preferred and were programmed to BIV. Quality of life was evaluated by one disease specific and one generic form - the Minnesota Living with Heart Failure questionnaire and the Karolinska questionnaire - in 30/35 patients with BiV at 9 (M9) and 12 months (M12) compared to Start CO.
Results: Significant and sustained benefits regarding the Minnesota form were seen at M9 and M12 compared to start CO. Results from selected dimensions of the Karolinska form are given in the figure.



QoL improvement

In conclusion: In parallel with a maintained clinical improvement, quality of life benefits were sustained over one year by biventricular pacing in these patients with severe heart failure, atrial fibrillation and intraventricular conduction delay.

P359 Long-term biventricular pacing decreases inducibility of ventricular arrhythmia in congestive heart failure

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Background: Biventricular (BV) pacing may improve systolic left ventricula function, functional status and well-being of patients with depressed left ver tricular function and interventricular conduction delay. These patients with cor gestive heart failure often have an indication for ICD implantation as well. Th aim of the present study was to evaluate whether long term BV pacing de creases inducibility of ventricular arrhythmias in these patients.
Methods: 10 patients treated with a combined BV-ICD device for dilated cai diomyopathy and at risk for ventricular arrhythmia were included. All patient underwent an electrophysiological (EP) study with ventricular programme electrical stimulation (PES), both before implantation of the BV-ICD device an after a period of at least 6 months of BV pacing. PES protocol was 8 beat driv train with basic cycle length 600, 500 and 400 ms and up to 3 extrastimuli wit minimal cycle length 200 ms.
Results: The patients included (7 M, age 64±12y) had dilated cardiomyopath (5 ischemic, 5 idiopatic) and interventricular conduction disturbances. Indica tions for ICD device were out of hospital cardiac arrest (n=6) or ventricula tachyarrhythmia (n=4). Antiarrhythmic drugs before BV-ICD (sotalol n=3, amio darone n=4) was not significantly changed at long term follow-up (sotalol n=4 amiodarone n= 3). Before BV-ICD implantation, sustained VT could be induce in 8 patients and nonsustained VT in one. After a period of 9.9 ± 4.1 months c BV pacing, VT was inducible in only 4 patients.
Conclusion: Long term BV resynchronisation therapy decreases the inducibil ity of VT from 90% to 40% ($p<0.05$). Resynchronisation therapy may have a antiarrhythmic effect.

P360 Long-term (2 years) clinical effects of permanent biventricular pacing in chronic atrial fibrillation. Results from the MUSTIC trial

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Background: Previous controlled and randomized studies have shown tha biventricular pacing improved functional status in patients with advanced hear failure, intraventricular conduction delay and left ventricular (LV) systolic dys function and stable sinus rhythm. However, results of permanent biventricula pacing in atrial fibrillation patients remain controversial.
The aim of the present study was to evaluate the long term clinical benefit o permanent biventricular pacing (follow up = 2 years) in atrial fibrillation patient included in the MUSTIC trial.
Method: The MUSTIC trial was a cross-over (2 x 3 months) designed study t assess the effect of biventricular pacing. After the two cross-over phases, the patient were followed every 3 months in the pacing mode selected according t their preference (biventricular or uni-right ventricular pacing).
43 patients in permanent atrial fibrillation (66 ± 9 years), all in NYHA class III with a mean LV ejection fraction (LVEF) of 25 ± 10% were included in this study. Baseline data were recorded after a 3 month period of heart rate control in most cases by radiofrequency AV node ablation, and uni-right ventricula pacing. After the completion of the cross-over phases, all patients but 4 were programmed in biventricular pacing mode.
Results:

	Baseline	1 year	2 years
Heart rate (bpm)	75±15	76±7	71±12
NYHA class	3±0	2.2±0.5*	2.2±0.5
6 min walk (m)	325±82	370±87*	362±99
Peak VO2 (ml/min/kg)	13±4	14±3.5	NA
QOL questionnaire	45±23	31±17*	32±20*
LVEF radionuclides (%)	26±7.7	30±8*	NA

* $p<0.01$ vs baseline, NA = not available

To date, 26 patients completed the 2-years follow-up.
Conclusion: These data suggest that biventricular pacing significantly im proves the quality of life and exercise tolerance over a 2 years follow-up ir advanced heart failure patients with permanent atrial fibrillation.

P361 Benefits of cardiac resynchronization therapy – results of the InSync and InSync ICD trials

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Background: The InSync & InSync ICD trials were each designed as a multicenter, randomized, double-blind controlled study to evaluate the safety and effectiveness of CRT in a large number of patients with advanced systolic heart failure, ventricular dysynchrony and, in the case of InSync ICD, an indication for an ICD.
Methods: 815 NYHA Class III and IV patients were successfully implanted with the InSync (n=453) or InSync ICD (n=362) systemand randomized to either the CRT OFF (control, n=401) or the CRT ON (treatment, n=414) group. Primary effectiveness endpoints in both studies were quality of life (QOL, as measured by the Minnesota Living with Heart Failure questionnaire), NYHA class and 6-minute hall walk distance (6MW). Key secondary endpoints included peak VO2/kg, exercise time, and LVEF.
Results: Effectiveness results comparing the median paired differences at baseline and 6 months are summarized in the table below.

	CRT ON	CRT OFF	P-value
QOL*	-18	-9.5	<0.0001
NYHA Class*	-1	0	<0.0001
6MW (meters)*	46	28	0.01
Peak VO2/kg (ml/kg/min.)	1.1	0.2	0.006
Exercise Time (sec.)	68.5	13	<0.0001
LVEF (%)	4.0	0.6	<0.0001

*Median paired difference

Conclusions: In patients with moderate to severe heart failure and LV dysynchrony, the InSync and InSync ICD trials have demonstrated that cardiac resynchronization is safe and improves functional status.

ARRHYTHMIAS MECHANISMS: CELLULAR ELECTROPHYSIOLOGY AND PATHOPHYSIOLOGY

P362 Pharmacological modulation of the pacemaker current (IF) in human atrial myocytes

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IF is an inward Na/K current, activated by hyperpolarization and responsible for the phase 4 of action potential; IF is constitutively expressed in human atrial myocytes (HuAM), where it is modulated by beta-adrenergic (βAR) and serotonin (5-HT4) receptors. Modulation of IF may play a relevant role in triggering human atrial arrhythmias. Recent data obtained by heterologous re-expression of human F-channels and 5-HT receptors suggest that differences exist in the pharmacological modulation depending on channel and receptor isoforms. In particular, 1) HCN1 isoform of the F-channel seems to be insensitive to cAMP and 2) 5-HT(4b), but not 5-HT(4a), isoform is coupled to both inhibitory (Gi) and stimulatory (Gs) G-proteins. However, the functional relevance of this different coupling has never been tested on native F-channels in human cells. The aim of this study was to investigate the pharmacological properties of IF in HuAM, by evaluating its modulation by cAMP cascade through β1AR, β2AR and 5-HT4 receptor stimulation.
Methods: Coupling of receptor subtypes with Gi was tested by incubating HuAM in 0.5 μg/ml pertussis toxin [PTX] (which inactivates Gi) for 3 hours at 33°C. Myocytes were isolated from specimens of right atrial appendages, collected during cardiac surgery procedures. All patients were in sinus rhythm. Myocytes were freshly utilised for patch clamp recording of IF in whole cell configuration.
Results: IF was recorded in 62 cells: its density was 28.1±2.8 pS/pF and midpoint activation voltage ($V\frac{1}{2}$) was -93±2 mV. β1AR stimulation was carried out by superfusing cells with isoprenaline (ISO, 1 μM) in the presence of the selective β2AR antagonist ICI 118,551 (50 nM); β2AR stimulation was obtained with 1 μM ISO plus the selective β1AR antagonist CGP 20712A (100 nM); 5-HT4 stimulation was obtained with 1 μM serotonin. All stimuli were able to cause a positive shift ($DV\frac{1}{2}$) of IF activation curve (β1AR $DV\frac{1}{2}$=16.3±2.2 mV n=13; β2AR $DV\frac{1}{2}$=11.5±1.6 mV n=13; 5-HT4 $DV\frac{1}{2}$=16±2 mV n= 15) ($p<0.0001$ versus corresponding controls), resulting in an increase of active current at voltage near to the physiological diastolic potential. All receptor subtypes also speeded up the rate of IF activation. Pre-incubation with PTX did not alter the pharmacological response of F-channel to β1AR ($DV\frac{1}{2}$[PTX]=14.4±2.5 mV), β2AR ($DV\frac{1}{2}$[PTX]=12.1±2.0 mV) and 5-HT4 stimulation ($DV\frac{1}{2}$[PTX]=16.8±1.8 mV) (NS versus no-PTX conditions for all).
Conclusions: IF is positively modulated by cAMP-coupled receptors, whose effect is unchanged by Gi blockade.

P363 S100A1 enhances the L-type Ca^{2+} current in murine cardiomyocytes

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Background: S100A1 is a Ca^{2+} binding protein of the EF hand-type with a muscle specific expression pattern. It displays highest protein levels in cardiomyocytes and has been found to be expressed as early as on day eight in the embryonic heart. Since S100A1 is known to be involved in the regulation of Ca^{2+} homeostasis we tested whether S100A1 also plays a role in regulating the L-type Ca^{2+} current (ICa) in murine cardiomyocytes. Methods and Results: Murine embryonic (E16.5) ventricular cardiomyocytes were coincubated with S100A1 (0.001-10μM) for 2 to 48h. The amplitude of peak ICa was significantly increased as early as 2h (+33.1±16.%, n=6, $P<0.05$) after the addition of S100A1, while current-voltage relationship and inactivation characteristics remained unchanged. Fluorescence- and capacitance measurements evidenced a fast translocation of rhodamine coupled S100A1 from the extracellular space into cardiomyocytes. S100A1 treatment did neither affect the functional expression of L-type Ca^{2+} channels (VDCC) nor cAMP levels. However, protein kinase inhibitor (PKI), a selective blocker of the cAMP-dependent protein kinase A (PKA), abolished the S100A1-mediated enhancement of ICa and measurements of PKA activity yielded a significant increase in S100A1-treated cardiomyocytes (53.7±7.4%, n=6). Conclusion: The Ca^{2+} binding protein S100A1 enhances ICa via increase of PKA activity. Thus, S100A1 enhances myocardial inotropy by augmenting transsarcolemmal Ca^{2+} influx.

P364 The human cardiac inwardly-rectifying K^+ channel Kir2.1b (hIRK) is inhibited by direct protein kinase C-dependent phosphorylation

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Introduction: For the stabilization of the resting membrane potential and in arrhythmogenesis, the native inward rectifier potassium current IK1 plays a critical role. Protein kinases A (PKA) and C (PKC) are activated in coronary artery disease and heart failure accompanied by life-threatening ventricular arrhythmias.
Methods: This study investigates the functional relationship between PKA, PKC and IK1 or its cloned correlate Kir2.1b (hIRK) with techniques of molecular electrophysiology.
Results: In whole-cell patch-clamp experiments with isolated human atrial cardiomyocytes, the IK1 current was decreased by 41%, when the unspecific activator of PKC, phorbol 12 myristate 13-acetate (PMA, 100 nmol/L) was applied. To study the effects of PKA and PKC on a cloned channel underlying parts of the native IK1, we expressed Kir2.1b (hIRK) heterologously in Xenopus oocytes and measured currents with the double-electrode voltage-clamp technique. PMA (100 nmol/L) decreased the current by an average of 68%, with an IC50 of 0.68 nmol/L. The inactive compound 4-alpha-PMA was ineffective. Thymeleatoxin and OAG, two specific activators of PKC, produced similar effects as PMA. Inhibitors of PKC, i.e. staurosporine and chelerytrine, could inhibit the PMA-effect (1 nmol/L) significantly. After mutation of the PKC phosphorylation sites (especially S64A and T353A), PMA became ineffective. Pharmacological activation of PKA increased the current. Mutation of the single PKA phosphorylation site on Kir2.1b could not establish any significant results.
Conclusion: The human IK1 current in isolated atrial cardiomyocytes and one of its underlying clones, the Kir2.1b channel, is inhibited by PKC dependent signal transduction pathways, possibly contributing to heart arrhythmias in patients with structural heart disease.

P365 Modulation of spontaneous activity in mouse ventricular myocytes by adenovirus-mediated gene transfer of Kir2.2 channels

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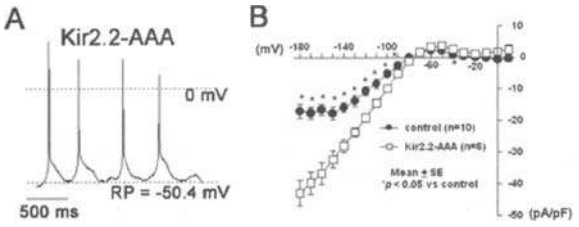
Purpose: To explore the feasibility of genetic modulation of intrinsic pacemaking activity of the ventricle, we investigated the effects of gene transfer of Kir2.2 channels to mouse ventricular myocytes.
Methods: wild-type Kir2.2 channels (Kir2.2-wt) and its dominant-negative mutant (Kir2.2-AAA: GYG motif of the ion selective filter was replaced by AAA) were incorporated into adenovirus vector. Cultured ventricular myocytes of neonatal mice were used for in-vitro transfection of Kir2.2-wt. Adult mice were used for in-vivo transfection of Kir2.2-AAA by a catheter-based method (Hajjar et al., 1998). Action potentials and IK1 were recorded using patch-clamp technique in a whole-cell mode.
Result: Regular spontaneous beating was observed in 12/20 (60%) control neonatal myocytes at 145 ± 10/min with resting membrane potential (RP) at -56.2 ± 3.2 mV. The Kir2.2-wt overexpressed myocytes showed less incidence of spontaneous beating (4/20 cells, 20%) at significantly slower rates (35 ± 2/min, n=4) and more negative RP (-72.3 ± 3.1 mV) (n=5, $p<0.05$). The ventricular myocytes isolated from control adult mice showed no spontaneous beating, whereas 30/100 (30%) myocytes from mice transfected with Kir2.2-AAA in-vivo showed spontaneous beating at 110 ± 10/min (Fig. 1A). The Kir2.2-AAA transfected myocytes had less negative RP (-53.8 ± 7.4 mV) and lower IK1 density (0.73 ± 0.36 pA/pF at -40 mV) than controls (-68.1 ± 0.8 mV, 2.54 ± 0.36 pA/pF) (n=8, $p<0.05$) (Fig. 1B).



Conclusion: The automaticity of ventricular myocytes can be regulated by adenovirus-mediated gene transfer of Kir2.2 channels, suggesting the feasibility of gene therapy for both brady- and tachyarrhythmias.

P366 Excitability restitution in fibrotic human myocardium depends on the architecture of fibrosis

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Progressive ventricular activation delay (PAD) starting at long coupling intervals of premature stimuli has been shown to correlate with sudden cardiac death in patients with heart disease. We studied PAD in 11 explanted hearts of patients undergoing heart transplantation and hypothesize that PAD depends on the amount and type of interstitial fibrosis.
Methods and results: Eleven hearts were studied (4 coronary artery disease, 1 hypertrophic cardiomyopathy and 6 dilated cardiomyopathy). Eight hearts were Langendorff-perfused, from the 3 remaining hearts superfused epicardial sheets (1 mm thickness) were taken and studied in a tissue bath. High resolution unipolar epicardial activation mapping (105 or 208 recording sites; interelectrode distance 0.8 or 0.5 mm, respectively) was carried out following premature stimulation in 11 hearts. Activation maps and conduction curves were constructed and correlated with histology. As a measure for PAD, the mean increase of delay (MID) was obtained from the conduction curves. Prominent increase of MID was associated with zones of patchy, dense fibrosis with long fibrotic strands and depended on the direction of propagation relative to fiber direction.. In contrast, MID was only marginally affected by short strands of fibrosis (diffuse fibrosis) with the same high density. The table shows the main results.

	Fibrosis(%)	MID(ms)	CVIIBCL(m/s)	CVIIS2(m/s)	CV=BCL(m/s)	CV=S2(m/s)
Patchy	21.8±13.8	18.4±5.8	0.28±0.07	0.05±0.01	0.57±0.13	0.31±0.12
Diffuse	20.7±13.7	5.0±1.3	0.24±0.04	0.17±0.06	0.58±0.15	0.41±0.22

Conduction velocity during BCL and after premature stimulation (S2) for different types of fibrosis. CVII and CV=: conduction velocity perpendicular (II) and parallel (=) to fiber direction during basic cycle length and S2

Conclusions: In chronically diseased human myocardium long fibrotic strands cause PAD starting at long coupling intervals of premature stimuli. MID depends strongly on the direction of the wave front with respect to fiber direction and on the architecture of fibrosis. These data suggest that patients with patchy fibrosis with long strands are more prone to develop VF than patients with diffuse fibrosis.

P367 Intercellular communication in connexin43 transfected skeletal myocytes

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Myocyte transplantation has been considered a potential therapy to repair damaged myocardium. In the attempt to create electrical coupling between cardiac and transplanted skeletal myocytes, we transfected Connexin43 cDNA (Cx43) into skeletal myocytes using a retroviral expression vector MLV-CX43-EGFP2, which produces 80% infection in these Cx43 transfected skeletal myocytes by FACS analysis of EGFP expression. We report here the results on the studies of the functional gap-junctional communication of Cx43 transfected skeletal myocytes.
2 skeletal myocyte preparations were studied: L6 cell line and primary rat skeletal myocytes. Cx43 transfected cells (Cx43) and the control cells (Cont.) were grown in culture dishes to confluence, and were placed on the stage of an epifluorescence microscope. Microelectrodes were filled with 5% fluorescence dye cascade blue. A 2-4nA current for 1min was applied to the electrode to deliver dye into the cell. Dye transfer to the adjacent cells was recorded using a DC 200 digital camera (Leica). The number of cells to which dye was transferred within 60 seconds with each injection was counted. Data were analysed statistically using T-test (two population t-test).
Four groups of experiments were carried out in this study: L6, non-transfected and transfected; Primary myocytes, non-transfected and transfected. Dye transfer occurred in 65.0% and 16.7% of L6 Cx43 and L6 Cont. respectively, and 64.7% and 13.3% of primary Cx43 and primary Cont. respectively. The number of cells to which dye was transferred with each injection ranged from 0-3 cells, and was significantly greater in the transfected culures (L6, P=0.001; primary P=0.026, table)

	L6 Cell Line N=18	Cx43 Cell Line N=20	Primary Cell N=17	Primary Cx43 Cell N=15
# Cells Dye Transferred (Mean ± SD)	0.17 ± 0.147	0.90 ± 0.621*	0.13 ± 0.124	0.70 ± 0.346*

* Compared with control, $P<0.05$

The results show Cx43 transfection induced gap junctional coupling and enhanced dye transfer in cultured skeletal myocytes, with the potential, therfore, of enhancing incorporation into the functional myocardial syncytium.

P368 Increased atrial tissue expression of angiotensin II type 1 receptor (AT-1) in an animal model of pacing induced atrial remodelling

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Recent studies in animal models of sustained rapid atrial pacing showed that angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. However no systematic investigation has been made of atrial tissue expression of angiotensin II type 1 receptor (AT-1) in this animal model. The present study was designed to assess atrial AT-1 receptor expression in the early stages of atrial remodeling in a canine model of prolongaded rapid atrial pacing.
Methods: Fifteen halothane-anesthetized adult beagle dogs underwent insertion of a transvenous lead at the right atrial appendage. Ten dogs were continuously paced at 400 bpm for 3 days and 5 dogs in sinus rhythm served as control. Right atrial effective refractory period (ERP) was measured at either baseline and after 3 days in both groups. Atrial tissue AT-1 receptor expression was determined in interatrial septum, lower right atrium, right and left atrial appendages by Western-blot and immunohistochemical staining. Additionaly fibrotic changes of the atrial myocardium were examined by conventional and electron-microscopy studies.
Results: At baseline study the right atrial ERP was similar in controls (136±15 msg) and paced dogs (120±20 msg). After 3 days of continuous pacing the ERP was significantly shorter than control (80±30 msg vs 140±10 msg; $p<0.03$). We found a basal AT-1 receptor expression in both right and left atrial myocardium. However atrial AT-1 receptor expressión increased almost 2-fold in dogs after three days of prolongaded rapid atrial pacing. This increasing was more manifested in the right than in the left atrium and more marked in the appendage and lower right atrium. These findings correlated with the expression levels of proteins detected by immunohistochemical stainig. In paced dogs, no evidence of increased extracelular fibrosis or connective tissue content was documented.
Conclusion: Rapid atrial pacing increases atrial tissue expression of angiotensin II type 1 receptor (AT-1) in early stages of atrial remodeling before appearance of fibrotic structural changes. The use of AT-1 receptor antagonist may be useful to prevent atrial fibrosis during structural remodeling of atrial fibrillation.

P369 Electrocardiographic evidence of Duchenne muscular dystrophy in a mouse model suggests a novel clinical diagnostic tool

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Objective: Record and analyze electrocardiograms (ECGs) in dystrophin-deficient (mdx) mice, a mouse model of Duchenne muscular dystrophy (DMD), to see whether they correspond to clinical observations in patients with DMD.
Methods: A new system for non-invasively recording ECGs in conscious mice (no anesthesia, no implants) and e-MOUSE ECG analyses software in male mdx (n=15) and C57 control (n=15) mice at baseline and in response to atropine (0.5 mg/kg, i.p.) and phenylephrine (3 mg/kg i.p.).
Results: We demonstrate that mdx mice have significant tachycardia, consistent with observations in Duchenne patients. Heart rate was nearly 15% faster in mdx mice (809 ± 5 bpm) than in control mice (706 ± 13 bpm, $P<0.01$). ECGs revealed significant shortening of the rate corrected QT interval duration (QTc) in mdx mice compared to control mice (55.5 ± 0.5 ms vs. 61.6 ± 1.5 ms, $P<0.05$). PR interval durations were shorter at baseline in mdx compared to control mice (27.2 ± 0.4 vs. 29.4 ± 0.5 ms, $P<0.05$). The muscarinic antagonist atropine significantly decreased heart rate and increased PR interval duration in all mdx mice but not in control mice. Compared to the effects in C57 mice, atropine administration in mdx mice led to significantly greater changes in HR (-90 ± 14 bpm vs. +21 ± 12 bpm, $P<0.05$) and significantly smaller changes in HRV (+0.1 ± 0.1 ms vs. -1.6 ± 0.7 ms, $P<0.05$). mdx mice administered phenylephrine demonstrated significantly smaller reductions in HR compared to C57 mice, (-132 ± 27 bpm vs. -312 ± 39 bpm, $P<0.05$). Pharmacological autonomic blockade and baroreflex sensitivity testing demonstrated an imbalance in autonomic nervous system modulation of heart rate, with decreased parasympathetic activity and increased sympathetic activity in mdx mice.
Conclusions: mdx mice have tachycardia and an autonomic nervous system imbalance affecting heart rate modulation, consistent with observations in Duchenne patients. The cholinomimetic effects of atropine in mdx mice but not in C57 control mice suggest a simple test that may be predictive of dystrophin-deficiency.

P370 A French hot spot in KCNQ1 at position 174 is associated with mild forms of congenital long QT syndrome

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Background: Long QT syndrome (LQTS) is characterized by QT prolongation on the surface ECG and ventricular arrhythmias responsible for syncope and sudden death. It is a heritable ion channel disease caused by mutations in genes encoding sodium or potassium ion channel subunits. Genetic abnormalities are most frequently found in the potassium channel genes KCNQ1 (LQT1) and HERG (LQT2).
Methods: The genotyped LQTS population included 90 LQT1 families, 40 LQT2 families and 6 LQT3 families. The phenotype of each subject was ascertained by clinical history, ECG and Holter recording. We analyzed the phenotype of the most frequent mutation in LQT1.
Results: Sixty-four mutations were identified in KCNQ1 among the 90 LQT1 probands. Arginine at position 174 was the most frequently mutated aminoacid (8 families, 33 carriers). R174 was replaced either by a cysteine (R174C) in 5 families (n=20) or by a histidine (R174H) in 3 families (n = 13). In one patient with congenital deafness R174C was homozygous, and in another case the mutation was associated with a second LQT1 mutation (R293C). Two probands out of 5 were asymptomatic and were diagnosed by routine ECG testing before DNA testing.There was no history of sudden death in these families. The phenotypes of R174C carriers were found to be milder compared to R174H carriers with regards to both QTc duration (449 ± 49 ms, n = 20, versus 484 ± 31 ms, n = 13) and to syncopes (3/20 versus 6/13).
Conclusions: R174 was the most frequently mutated amino acid in the French LQT1 population. The R174C mutation was clearly associated with a mild phenotype, whereas R174H presented with a higher penetrance. Such mutations can be a precipitating factor for ventricular arrhythmias in the setting of QT prolonging drugs.

P371 Paced electrogram fractionation in symptomatic and asymptomatic long QT patients

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Background: Paced ventricular electrogram fractionation (PEF), increased electrogram duration and number of potentials following premature paced extrastimuli related to inhomogenous conduction are strongly associated with VF in patients with hypertrophic cardiomyopathy. Aim of study was to analyse PEF in pts with long QT syndrome (LQTS). Material and methods: PEF was studied in 30 patients: 26 females and 4 males, aged 11-56 (mean 27), with LQTS. All pts had QTc > 440 ms, and no structural heart diseases. Group consisted of: 10 pts after aborted VF, 6 pts with syncopies and 14 asymptomatic patients. Controls (12 pts) were studied after diagnostic, normal EP. Stimulation protocol was S1S2 490 ms and S1S2 450-220 ms, shortening 1 ms every third beat. Potentials of each electrogram obtained from recording electrodes were plotted against S1S2. Characteristics of the pts were (average from all electrodes): value of S1S2 at which delay occurred and corresponding increase of duration of electrogram. Multivariate discrimination analysis and Fisher's exact test for statistics were used. Results: All LQTS patients had increased fractionation compared to controls (328,4+21,4ms/13,7+8,7ms vs. 270+11,4ms/3,1+3,7ms, $p<0,01$). Fractionation was higher in LQTS pts with VF than in all other LQTS pts (339+23,5ms/15,1+9,8ms vs. 322+19ms/13,2+8,9ms, $p<0,04$). Results showed increase in electrogram delay with an increased number of potentials in symptomatic, especially VF, pts. Conclusions: Patients with the LQTS demonstrated large intraventricular conduction delays, strongly visible with the symptoms aggravation, that is compatible with functional re-entrant substrate theory and suggests that PEF analysis may be useful in risk assessment in LQTS patients. Observed delays may be result of axial block due to local refactoriness and consequent slowed transverse and anisotropic activation.

P372 Gender-related proarrhythmia in a rabbit model of LQT2 and LQT3

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Recent clinical observations indicate that female gender is associated with a high risk of developing cardiac arrhythmias especially of the torsade de pointes (TdP)-type in humans. We therefore sought to investigate gender differences in a previously developed rabbit heart model of TdP. Methods and Results: In 40 Langendorff-perfused rabbit hearts, the IKr-blocker erythromycin (E; 150-300μM) as well as veratridine (V, 0.1-0.5μM), an inhibitor of sodium channel inactivation, led to significant increase in QT-interval and monophasic action potential (MAP) duration in male (E; n=13, V: n=9) as well as in female (E: n=11, V: n=7) hearts and thereby mimicked long QT (LQT)2 and LQT3 syndrome. In bradycardic (AV-blocked) hearts, up to eight simultaneous epi- and endocardial MAP demonstrated a significant increase in dispersion of repolarization in male and female hearts. There was no significant difference in QT-interval or mean APD50 or APD90 between female and male hearts at baseline or after infusion of E and V. In E-treated hearts 6 (46%), 9 (69%) and 10 (76%) of 13 male hearts showed early afterdepolarizations (EAD) and developed TdP at the three concentrations. In female hearts, 9 (82%) 11 and 11 of 11 hearts showed EAD and TdP (p=ns as compared to male). In V-treated-hearts, 1 (11%), 8 (89%) and 9 of 9 male hearts showed EAD and developed TdP at the three concentrations. In female hearts, 1 (14%) 7 and 7 of 7 hearts showed EAD and TdP (p=ns as compared to male). Conclusion: Rabbit hearts show a high incidence of proarrhythmia of the TdP-type in a model of LQT2 and LQT3 and are thereby an excellent model for drug screening. Due to the high incidence of proarrhythmia there is only a slight gender difference in this animal model.

P373 Efficacy of antiarrhythmic therapy in patients with effort polymorphic ventricular arrhythmias and ryanodine receptor gene (RyR2) mutations

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Background: effort induced polymorphic ventricular arrhythmias (PVA) have been recently proved to be linked to ryanodine receptor gene (RyR2) mutations. Beta-blocker therapy seems to play a role in avoiding or reducing the incidence of arrhythmias and to prevent sudden death (SD).
Aim of the study: to evaluate the efficacy of therapeutic strategies in the long term follow-up of patients with PVA associated with RyR2 mutations.
Materials and methods: in 1985 a family in which four cases of juvenile SD had occurred was studied. In all family members genetic study was carried out. The family consisted of 26 living subjects belonging to three generations (11 M, 15 F, mean age 32±15 yrs). Thirteen subjects (6M, 7F, mean age 30±16 yrs) showed effort induced PVA (non sustained ventricular tachycardia or premature ventricular beats); they all underwent beta-blocker therapy (acebutolol 200 to 600 mg daily) and were strongly advised to avoid strenuous physical exercise. Stress test was undertaken to evaluate the efficacy of therapy.
Results and follow-up: DNA testing proved the presence of RyR2 mutation N2386I in 14 subjects (6M, 8F, mean age 29±17 yrs), all with PVA except one (female, 10 yrs old). Five subjects had syncopal episodes and three experienced dizziness before the beginning of antiarrhythmic therapy. In four subjects who were younger than 12 at the time of the first visit, arrhythmias appeared during the follow-up (mean age 14±1 yrs). Beta-blocker therapy caused the disappearance of PVA in 20% of cases, while in the remaining subjects arrhythmias appeared at a higher level of load and consisted of isolated ventricular premature beats in the majority of cases. During follow-up (2 to 16 yrs, mean 9) no patient had syncopal episodes or died suddenly.
Conclusions: the long term follow-up of this family demonstrates the efficacy of beta-blocker therapy in reducing PVA and preventing SD. The therapeutic strategy in asymptomatic carriers of RyR2 mutations remains a challenge, since SD may be even the first manifestation of the disease.

P374 A deletion in the calsequestrin gene (CASQ2) causes the autosomal dominant form of catecholaminergic polymorphic ventricular tachycardia

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disease characterized by adrenergically (emotion and/or exercise) induced syncope and sudden death manifesting during childhood and adolescence in the absence of cardiac structural abnormalities. The disease is mainly transmitted with an autosomal dominant pattern even if a rare autosomal recessive form has been reported. We recently demonstrated that the cardiac ryanodine receptor gene (RyR2) is a gene involved in the autosomal dominant form of the disease, while Lahat et al identified mutations in the Calsequestrin gene (CASQ2) in the rare autosomal recessive variant. Calsequestrin is a component of the calcium release complex of the sarcoplasmic reticulum and is functionally linked to RyR2. Here we provide the first evidence of a link between the autosomal dominant form of CPVT and the CASQ2 gene. An eleven year old Caucasian female with history of syncope was referred for evaluation. Baseline ECG was unremarkable with normal QT interval and runs of fast non-sustained polymorphic ventricular tachycardia were elicited at exercise stress test. The 45 year old mother had experienced repeated syncopal episodes triggered by physical activity and she also presented ventricular arrhythmias at exercise stress test. No signs of structural heart disease were present in both patients. The diagnosis of autosomal dominant CPVT was established and molecular screening of the RyR2 gene was performed on genomic DNA. No mutations were identified in the open reading frame of RyR2 while molecular screening of the CASQ2 gene led to the identification of a 16 bp deletion creating a frameshift and a truncation of the distal 2/3 of the protein leading to haploinsufficiency. This mutation was present in the proband and her mother in the heterozygous state but not in the unaffected father and in 400 control individuals.
In summary present data suggest that CASQ2 is a novel gene responsible for the autosomal dominant variant of CPVT further supporting the concept that arrhythmias in CPVT are caused by abnormal intracellular calcium handling.

P375 QT dispersion in Arg 403 Gln missence point mutation of beta-myosin-heavy-chain in hypertrophic cardiomyopathy families

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Backgraund: QT dispersion (QTD) is regarded as an important prognostic factor in hypertrophic cardiomyopathy (HCM). Prolongation of QTD may be variable in different HCM genotypes. The aim of this study is the examination of the degree of QTD in Arg 403 Gln missence point mutation of beta-myosin-heavy-chain (MHC) in HCM families.
Methods: The study was carried out on 17 HCM families with 28 cases of HCM (12 females, 16 males) and 90 phenotype-negative relatives (56 females, 34 males), thus on a total of 118 cases screened by history, physical examination, ECG, two-dimensional echocardiography and genetic examination. QT interval was measured in all leads from a standart 12-lead ECG. QTD was calculated as the maximal difference between QT intervals in any two leads, and corrected for heart rate (QTcD) with Bazett formula.
Results are shown in table.

	HCM Arg 403 Gln (+) n=7	HCM Arg 403 Gln (-) n=21	p value	Relatives Arg 403 Gln (+) n=13	Relatives Arg 403 Gln (-) n=77	p value
QTD (msec)	50±10	77±35	0.029	40±11	35±13	NS
QTcD (msec)	44±22	73±36	0.03	41±21	31±17	0.028

Conclusion: QTD and QTcD were significantly shorter in the patients with positive Arg 403 Gln missence point mutation of beta-MHC, although poor prognosis is frequently seen in this mutation. However, in the healthy relatives group, the QTcD value was significantly higher in those with positive mutation. As a result, we could not prove QTD as a significant indicator of Arg 403 Gln mutation.

P376 The role activation of sarcolemmal ATP-sensitive potassium channels play in ischaemic ST-segment changes and ventricular fibrillation

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It is well established that myocardial ischemia is accompanied by characteristic changes in the ST-segment of the ECG. However, the cellular events that are responsible for these ECG changes remain to be identified. The activation of sarcolemmal ATP-sensitive potassium (KATP) channels during myocardial ischemia has been shown to lead to potassium efflux with corresponding reductions in action potential duration. The resulting heterogeneity in repolarization could contribute to both the ECG changes and malignant arrhythmias induced by ischemia. To test this hypothesis, ischemia was induced a 2 min occlusion of the left circumflex coronary artery during the last min of exercise in dogs with healed myocardial infarctions. The exercise plus ischemia test provoked both significant (ANOVA, $P<0.01$) ST-segment depression (-6.5 ± 0.8 mm) and ventricular fibrillation in these animals (n=29). On subsequent days, the exercise plus ischemia test was repeated after pretreatment with one of the following KATP channel antagonists: sarcolemmal selective antagonists (HMR 1098, 3.0 mg/kg i.v., n=13) and HMR 1402 (3.0 mg/ kg i.v., n=4); mitochondrial selective antagonist 5-hydroxydecanoic (5-HD, 30 mg/kg i.v., n=5), or non-selective antagonist glibenclamide (1.0 mg/kg i.v n=7). Glibenclamide (-2.7 ± 1.5 mm), HMR 1098 (-3.1 ± 1.2 mm), HMR 1402 (-1.8 ± 1.9 mm), but not 5-HD (-4.5 ± 1.3 mm), significantly attenuated the ischemic ST segment changes and protected against ventrciular fibrillation (HMR 1098, 11 of 13; HMR 1402, 4 of 4; glibenclamide, 6 of 7; and 5-HD, 0 of 5 animals protected). In a similar manner, a 30 min occlusion of the left anterior descending artery occlusion followed by reperfusion in anesthetized (alpha-chloralose/urethane) dogs elicited significant reductions is the ST-segment throughout the ischemic period (-4.3 ± 0.9 mm, n=3) that were reduced by HMR 1098 (-1.6 ± 0.6 mm, n=5), HMR 1402 (-0.7 ± 0.7 mm, n=3) and glibenclamide (-1.0 ± 0.2 mm, n=3). In contrast to the lethal arrhythmias induced during ischemia, these drugs failed to prevent the ventricular fibrillation induced by reperfusion in any animal. These data suggest that the activation of cardiac sarcolemmal ATP-sensitive potassium channels may be responsible for the ST-segment changes induced by myocardial ischemia. These data further suggest that the activation of ATP-sensitive potassium channels plays a critical role in the induction of ventricular fibrillation during ischemia but not during reperfusion.

P377 Amiodarone-induced post-repolarization refractoriness prevents induction of ventricular fibrillation in the isolated rabbit heart

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It is still incompletely understood why amiodarone is such a potent antiarrhythmic drug. Sodium channel blockers prevent induction of ventricular fibrillation by inducing post repolarization refractoriness (PRR), but this antiarrhythmic effect is offset by conduction slowing (Circulation 97: 2567-2574). We studied to which extent amiodarone induces PRR and conduction slowing and related these effects to induction of ventricular arrhythmias.

The hearts of 13 amiodarone-pretreated (50mg/kg po for 6 weeks) rabbits and 14 controls were isolated and 8 monophasic action potentials were simultaneously recorded from the epicardium and endocardium of both ventricles. Steady state action potential durations (APD), activation times, refractory periods (ERP), and dispersion of APD were determined and digitally analyzed during programmed stimulation. Burst stimuli (20ms burst cycle length (CL), 5s duration, 2-10 x stimulation threshold) were applied to induce ventricular fibrillation.

Amiodarone prolonged APD at 50, 70, and 90% repolarization by 12-15ms at CL from 200-600ms (all $p<0.01$), but did not significantly change activation times or dispersion of APD. During programmed stimulation, amiodarone prolonged the shortest S2-induced APD and prolonged ERP more than APD, resulting in PRR (APD90 minus ERP Amio: 14±10ms, $p<0.05$). During burst stimulation, amiodarone induced even more PRR (Amio: 40±15ms vs. Base: 22±13ms, $p<0.05$) and reduced the inducibility of ventricular arrhythmias by 40% ($p<0.05$ vs. base). At high burst strengths, monomorphic ventricular tachycardias were induced instead of ventricular fibrillation in 35% of bursts ($p<0.05$ vs. base). PRR during burst stimulation protected against induction of arrhythmias at baseline and with amiodarone, while lack of PRR was associated with induction of ventricular fibrillation ($p<0.05$).

Conclusions: Chronic amiodarone treatment causes post-repolarization refractoriness without relevant conduction slowing. This effect prevents the induction of ventricular fibrillation and, evenly important, converts induced arrhythmias from ventricular fibrillation to monomorphic ventricular arrhythmias.

P378 Comparison of the electrophysiological effect on atrial myocardium between Ic antiarrythmic drugs, pilsicainide and flecainide

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The purpose of this study is to compare the effect of Ic-antiarrhythmic drugs on atrial electrophysiological characteristics. Pilsicanide is known as the pure Na channel blocker and flecanide is well known as class IC drug. Method: Subjects were 22 patients (51±13 years-old: P-group) in whom pilsicainide was administrated intravenously (1mg/kg/10min.) and 38 patients (49±15 years-old: F-group) in whom flecainide was administrated intravenously (2mg/kg/10min.). Atrial effective refractory periods (A-ERP), intra-atrial conduction time (CT), max intra-atrial conduction delay (max CD), repetitive atrial firing zone (RAFZ), fragmented atrial activity zone (FAZ), intra-atrial conduction delay zone (CDZ) were measured before and after drugs. CT was defined as the interval from the stimulus to the atrial deflection at the distal portion of the coronary sinus. Conduction delay (CD) was defined as the difference of CTs at between extrastimulus and basic cycle length. Positive conduction delay was defined as the increase in CT at extrastimulus $\geq$20 ms, comparing to CT at basic cycle length. The CDZ was defined as the range of the coupling interval, that shows positive conduction delay. RAF was defined as the occurrence of two or more premature atrial complexes. The presence of fragmented atrial activity (FAA) was defined as duration of A2/duration of A1 $\geq$150%. The FAZ was defined as the range of the coupling interval that resulted in FAA. Results: Pilsicainide and flecainide significantly prolonged A-ERP (210±27ms to 245±37ms; $p<0.001$, 217±32ms to 242±35ms;$p<0.001$, respectively) and CT (128±33ms to 160±40ms; $p<0.001$, 125±21ms to 154±28ms; $p<0.001$, respectively). The percentage of prolongation of A-ERP was 17±15% in P-group and 13±17% in F-group. The percentage of prolongation of CT was 26±15% in P-group and 24±13% in F-group. RAFZs were significantly improved in both group (22±25msec to 6±28msec;$p = 0.014$, 21±27msec to 11±22msec; $p = 0.039$, respectively). However, Max CD was shortened by pilsicainide, but not by flecainide (67±13msec to 52±33msec in P-group ($p = 0.027$) and 65±25msec to 61±28msec in F-group ($p = 0.383$)). FAZ and CDZ were improved in P-group (27±33ms to 12±33ms;$p = 0.011$, 54±28ms to 43±35ms, $p = 0.075$, respectively), but not in F-group. Conclusions: These data may indicate the possibility that the effect of pilsicainide on atrial vulnerability is stronger than that of flecainide.

P379 Effects of K (ATP) channel blocker on monophasic action potential and coronary flow in Langendorff-perfused guinea pig hearts under hypoxia

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ATP-sensitive potassium (K(ATP)) channels are present in the sarcolemmal membrane of cardiac muscle as well as in smooth muscle cells of coronary arteries. The channels are activated under hypoxic and ischemic conditions. In coronary arteries there is some residual activity during normoxia. Selective blockade of K(ATP) channels in the sarcolemmal membrane of cardiac myocytes was shown to prevent ventricular fibrillation in a dog model of sudden cardiac death (Billman et al. 1998 J. Pharmacol. Exp. Ther. 286:1465-1473). Blockade of K(ATP) channels in coronary arteries reduces the coronary flow and consequently, the supply with oxygen and substrates. Therefore, the aim is to develop selective blockers for the sarcK(ATP) with little effect on coronary flow as novel antiarrhythmic drugs.

We used a Langendorff-model of isolated perfused guinea pig hearts in which both effects could be compared. For sarcK(ATP)channels, the duration of the monophasic action potential at 90% repolarisation (MAPD) was recorded during low flow ischemia (1.2 ml/min, oxygen-free). The effects on the coronary flow were tested by perfusion at constant pressure (55 mmHg) with hypoxic buffer solution (gassed with 20% instead of 95% oxygen).

Results: For glibenclamide, repaglinide, HMR 1402 and HMR 1098 the half-maximal inhibition of the ischemia-induced shortening of the MAPD was 95 nM, 74 nM, 110 nM and 550 nM, respectively, whereas half-maximal inhibition of the hypoxia-induced increase in coronary flow was 25 nM, 220 nM, 9.7 μM and > 10 μM, respectively. The sulfonylureas glibenclamide as well as the carboxylic acid repaglinide are potent blocker both of the sarcK(ATP) channel, and the vascular K(ATP) channel. In contrast, the sulfonylthiourea HMR 1402 is nearly as effective as glibenclamide on inhibition of MAPD shortening, but for reduction of the coronary flow a 88fold higher concentration of HMR 1402 is necessary. The sulfonylthiourea HMR 1098 is somewhat less effective on the sarcK(ATP) channel but has no significant effect on K(ATP) channels in coronary arteries at concentrations up to 10 μM.

In conclusion, the Langendorff-perfused guinea pig heart is a good model to study the effects of K(ATP) channel blocker on the cardiac monophasic action potential and on the coronary vascular system. It could be confirmed that glibenclamide and repaglinide are potent, but unselective blocker. HMR 1098 and HMR 1402 show good selectivity to the cardiac K(ATP) channel, and therefore, are considered as novel drugs for the development against ischemically induced sudden cardiac death.

P380 Conduction delay within the coronary sinus in humans: implications for atrial arrhythmias

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Myocardial connections between coronary sinus and left atrium have been described in humans. Their conduction properties and potential arrhythmogenicity in patients with and without paroxysmal atrial fibrillation (PAF) are unknown.

Methods: Twenty-one patients (pts) with PAF, 32 pts with other arrhythmias, and 25 pts without arrhythmia, underwent catheter mapping of the CS from the distal, superoposterior part to the ostium during sinus rhythm, CS pacing, and right atrial pacing.

Results: Discrete double potentials or fractionated electrograms, indicative of delayed conduction, were recorded during proximal coronary sinus or right atrial pacing in 14 (66.7%), 11 (34.4%), and 5 (20.0%) pts, respectively ($P=0.004$). In 29 pts, double potentials were recorded at the distal, superoposterior CS, in 3 at mid-CS and in 4 at the ostium. Spontaneous or induced atrial tachyarrhythmias were recorded in 18 (85.7%), 12 (37.5%), and 2 (8.0%) pts in the three groups, respectively ($P<0.001$) and were originating from the CS in 6, 3, and 0 patients, respectively ($P=0.010$).

Conclusions: Recording of double potentials is possible within the CS, particularly at its distal, superoposterior part, near the left superior pulmonary vein. Their prevalence is higher in patients with PAF than in subjects with other or no arrhythmias and their presence denotes possible delayed conduction and substrate for atrial arrhythmias.

P381 A prospective study of atrial fibrillation after acute myocardial infarction: multivariate risk analysis using P-wave duration on SAECG, P-wave dispersion and clinical variables

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Purpose: P-wave duration on SAECG (PWD) and P-wave dispersion on standard ECG (Pd) are markers of intra-atrial conduction disturbances. Purpose of this study: to evaluate prospectively whether PWD and Pd can predict development of AF in patients (pts) with AMI.
Methods. Study population: 130 pts with AMI (100 men, 30 women, aged 56,9±12,3). Assesed parameters: Pd=Pmax-Pmin in the surface ECG; pts during first 24-hours in hospital underwent SAECG from XYZ leads, PWD signals at noise < 0,4mV analysed.
Results: 22 (16,9%) pts developed AF. Pd was more prolonged in the pts with AF than in those without AF (34,47 vs 19,68ms, p<0,05). PWD was longer (131,94 vs 116,24ms; p<0,05) in pts with AF. PWD>125ms and Pd>25ms defined pts at high risk of AF in optimal spec/sens ratio.

	sensivity	specifity	ppa	npa	OR(95%CI),p<0,05
PWD>125ms	74%	77%	40%	92%	6,2(1,4-26,5)
Pd>25ms	81%	82%	53%	96%	23,5(5,5-100,6)

*ppa/npa = positive/negative predictive accurancy; OR = odds ratio; CI = confidence interval

Univariate anlysis variables associated with development of AF: age>65, Killip class III-IV, PWD>125ms, and Pd>25ms. Stepwise logistic regression analysis showed that age>65, PWD>125ms and Pd>25ms were independently associated with AF.Conclusions: PWD and Pd both measured in a very early period of AMI are useful in predicting AF.®

P382 Study of initiation and perpetuation of atrial fibrillation in a computer model of human atria based on magnetic resonance images

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While different mapping techniques have provided significant information on the electrophysiological processes associated with atrial fibrillation (AF), the mechanisms underlying its initiation and perpetuation remain unclear. Hence its treatment is sometimes based on empirical considerations. A computer model of atrial fibrillation offers the advantage of providing reproducible information at multiple biological scales. Furthermore, it is possible with such a model to study separately the parameters leading to the initiation and perpetuation of AF.
Methods: An electro-anatomical model of human atria has been developed using an ionic-based membrane model and geometry derived from segmented MR images of human atria. The three-dimensional surface includes obstacles corresponding to the location of major vessels and valves. The main advantage of this model is its ability to simulate several seconds of AF in a tissue with realistic size and membrane kinetics. Clinically relevant protocols, such as single-site burst pacing, were used to initiate AF (defined as multiple reentrant wavelets). The model outputs both transmembrane potential maps and electrograms at any location, facilitating comparisons of simulation results to experimental clinical data. The dynamics of AF was investigated for different action potential durations (APD) and restitution properties.
Results: In our baseline model with normal conduction velocity and APD, AF was inducible but non sustained. Initiation was dependent on the restitution properties. The first wavebreaks tend to occur in regions where the curvature varies rapidely (righ and left appendages for example). However, AF converted to sinus rhythm after a few seconds, usually preceded by a gradual reorganization and a decrease in the number of wavelets. Time to self-termination was difficult to predict from potential maps or indices of organization such as the number of wavelets. However, significant longer runs of AF could be obtained by an abrupt reduction of APD, corresponding to electrical remodeling. The influence of APD on the average duration of AF was computed.
Conclusion: The maintenance of multiple wavelets appears to be a consistent feature of AF. The simulations studies suggest that the restitution dynamics (describing the dependence of the action potential duration on the previous diastolic interval) and the APD may play a crucial role in determining initiation and duration of AF. This new computer model therefore allows us to confirm existing hypothesis and develop new concepts in AF.

P383 Time interval from the initiation of the P wave to the start of left atrial appendage ejection flow predicts atrial fibrillation recurrence

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Purpose: The rate of paroxysmal and persistent atrial fibrillation (AF) recurrence is high and unpredictable. This study investigates the ability of a novel method based on the measurement of the time interval from initiation of the electrocardiographic P wave to the start of left atrial appendage (LAA) ejection flow (P-LAA time) in predicting the risk of AF recurrence. P-LAA time was thought to reflect the interatrial conduction time which may be considered as a predictor of AF recurrence.
Methods: Fourty-five consecutive patients (age:61±11, 20 male) with newly diagnosed AF (AF duration: 132±725 hours) who converted to sinus rhythm spontaneously or with cardioversion were studied prospectively.
Real-time, simultaneous tracings of electrocardiogram and transesophageal Doppler recordings of the left atrial appendage flow was obtained in each patient. The time interval from the initiation of the electrocardiographic P wave to the start point of Doppler echocardiographic left atrial appendage ejection wave was measured (P-LAA time). This time interval was thought to reflect the interatrial conduction time; since the beginning of P wave is recorded when the depolarization first begins in the right atrium close to sinus node, and ejection of left atrial appendage which is quite away from sinus node, can only occur after the propagation of impulses up to left atrial appendage. Various clinical and echocardiographic parameters (age, sex, left and right atrial dimensions and areas, left and right atrial volumes, spontaneous echo contrast grade in LAA, flow velocity profiles and fractional area shortening of LAA)were analyzed with multiple regression analysis to identify the major predictors of AF recurrence.
Results: The patients were followed for a period of 163±72 days for the recurrence of AF. AF recurred in 17 (38%) patients after a mean time of 81±67 days. P-LAA time was significantly higher in patients with AF recurrence (123±36 vs. 92±24 msec, p=0.0047) and multiple regression analysis revealed that P-LAA time was the only significant independent predictor of AF recurrence (p=0.046). Left and right atrial dimensions, markers of LA and LAA mechanical function and other clinical factors were not identified as independent predictors of AF recurrence.
Conclusion: The results of the current study indicates that P-LAA time, which is thought to reflect interatrial conduction, may be considered as a reliable, independent predictor of AF recurrence.

P384 The increase of the atrial pacing ratio determines the antiarrhythmic effect of atrial overdrive pacing – experiences from the PROVE study

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The PROVE study intended to assess the benefit of fixed overdrive pacing in the prevention of atrial arrhythmias (AA). This sub-analysis is focused on the influence of the increase of the atrial pacing (Ap) ratio in patients implanted with dual-chamber pacemakers (ELA Talent DR 213).
Methods: AA burden was assessed by using appropriate Fallback Mode Switch episode (FMS) and atrial bursts documented by the pacemaker. After 1 month of monitoring, patients with >2 FMS were submitted to the following randomized therapies (T), each with a duration of 3 months. T1: basic rate (BR) = mean atrial rate + 10 bpm, rest rate (rR) = 60 bpm; T2: BR = rR = 60 bpm. The population was divided into 2 groups (G) according to the increase in Ap between the two therapies, compared to the median: GI: <15%, GII: >15%.
Results: Among 33 patients (15 males, 71±7 years), 4 presented with an AV-Block (AVB), 10 with a Sinus Node Dysfunction (SND), 9 a Brady-Tachy Syndrome (BTS), 9 AVB±SND±BTS and 1 AV node ablation.

Increase of the atrial pacing ratio

		threapy 1	therapy 2	p*
Group I (n=16)	mean Ap ratio	91 ± 10	88 ± 12	ns
	mean number of FMS	65 ± 97	62 ± 93	ns
	mean number of A bursts	318 ± 680	386 ± 693	ns
Group II (n=17)	mean Ap ratio	80 ± 10	49 ± 18	0001
	mean number of FMS	12 ± 21	50 ± 92	01
	mean number of A-bursts	109 ± 154	243 ± 361	03

Conclusion: Our results suggest that overdrive pacing is efficient in preventing AA only if it can significantly increase the atrial pacing ratio.

P385 Heart rate turbulence in patients with acute myocardial infarction: Impact of ischaemia and reperfusion

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Introduction: It has been shown that decreased heart rate turbulence (HRT), a surrogate marker for reflectoric parasympathetic activity, is associated with an increased risk of subsequent mortality in patients in the chronic phase after acute myocardial infarction (AMI). However, the impact of successful reperfusion therapy on HRT and the course of HRT from the acute to the chronic phase in AMI has so far not been investigated.
Methods: Therefore we prospectively enrolled 187 patients undergoing successful direct PCI (TIMI 2 and 3) for a first AMI. Turbulence onset (TO) and turbulence slope (TS) were determined after single ventricular premature beats in the time interval before reperfusion (I.), within the initial two hours after reperfusion (II.), and within the time period from hour 12 to hour 24 after reperfusion (III.) from 24-hour-Holter-ECG-recordings initiated on hospital admission. On day ten after AMI, TO and TC were again determined from an additional 24-hour-Holter-recording (IV.). A total of 133 patients fulfilled the clinical and technical inclusion criteria.
Results: There was a significant increase of TO and TC after reperfusion, followed by a constant moderate rise of both parameters within the observation period (table).

HRT before and after reperfusion in AMI

HRT variable	I.	II.	III.	IV.
Turbulence onset (%)	-0.25±3.3	-1.56±2.6 **	-1.76±2.8 #	-1.94±2.7 ¶
Turbulence slope (ms/RR)	15.9±14.6	18.9±17.7 **	19.7±16.1	22.6±18.1 ¶

** p<0.001 for I. versus II.# p<0.05 for II. versus III.¶ p<0.05 for III. versus IV.

Conclusions: The rise of HRT after successful reperfusion may be a previously unreported beneficial effect of direct PCI for AMI, reflecting a significant increase of the cardioprotective, reflectoric parasympathetic activity. Furthermore, there is a dynamic change of HRT within the phases of AMI. These findings have to be considered using HRT as a post-infarction risk-stratifier.

P386 Temporal distribution of ventricular fibrillation occurrence during acute myocardial ischaemia

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Background: The temporal distribution of ventricular fibrillation (VF) during myocardial ischemia in man is unknown. The available data are scarce and often obscured by immediate medical interventions. In large animals, ischemia-induced VF develops in two separate phases that have different electrophysiological mechanisms (phase 1A, related to reduced excitability and phase 1B, related to partial cellular uncoupling). We hypothesized that a 1B phase of VF is present in man. Therefore, we retrospectively investigated the time course and mode of onset of VF in a cohort patients with chest pain in the pre-thrombolytic era.
Methods: Between September 16 1980 and July 17 1983, 7026 patients with chest pain were investigated in the Amsterdam region, of whom 2258 had a myocardial infarction. A single lead ECG was recorded during 60 minutes from arrival of the ambulance onward. Forty-two of the infarct patients (1.9%) developed VF. Here, we studied ECGs at 25 or 50 mm/s of 32 patients (10 patients were excluded: 5 developed VF before ECG recording started, 2 had asthma cardiale, of 3 data were absent or incomplete). Eight patients received lidocaine (400 mg, intramuscular). Recording started 92±12 (mean±SEM) minutes after onset of complaints.
Results: VF occurred in 16% of patients within the first hour, in 38% between 1-2, in 25% between 2-3, and in 22% after 3 hours after onset of complaints, i.e. after onset of ischemia. An R-on-T premature beat with a coupling interval of 306±17 ms induced VF in 19 cases (59%), whereas a late premature beat (coupling interval 397±22 ms, p<0.01 vs R-on-T) preceded VF in 8 cases (25%). One patient had a 30-second episode of ventricular tachycardia before onset of VF. ST shift was present in 25 patients (elevation in 11 patients, depression in 14 patients. Note that a non-standard lead was recorded), and the ST segment was unchanged prior to VF in 4 patients. ST segment shift normalized in 4 patients before VF occurred, consistent with cellular electrical uncoupling.
Conclusions: Although information on the very early (phase 1A) occurrence of VF lacks in this study; VF occurrence peaked between 1 and 2 hours after onset of ischemia, indicating the presence of a 1B phase of VF. Normalization of ST segments prior to VF indicates partial intact cellular coupling and further supports the presence of a 1B phase. The possible presence of two phases of VF with different electrophysiological mechanisms merits further investigation and might provide future preventive therapies for this lethal condition.

P387 Wavelet analysis of heart rate variability before ventricular arrhythmias retrieved from implantable cardioverter-defibrillators

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Background: changes in autonomic tone leading to ventricular arrhythmias may be studied by heart rate variability (HRV). Wavelet transform is well adapted for analysis of non-stationary signals, such as heart rate recordings. Instantaneous High-Frequency (HF 0.15~0.4 Hz) components reflect vagal activity, while Low-Frequency (LF 0.04~0.15 Hz) components are under the influence of both sympathetic and parasympathetic tone. Thus, an increased LF/HF ratio may indicate increased sympathetic activity or decreased vagal tone.
Methods: 30 patients (mean age 61 years, 27 males) with ischemic heart disease implanted with a Biotronik Phylax XM® or Mycrophylax Plus® defibrillator with extended memory and having had appropriate electrical therapy for a ventricular arrhythmic event were studied. Two continuous recordings during 80 minutes were obtained from each patient: 1)during a routine visit and 2)preceding the ventricular arrhythmic event. Each recording was split into 10-minute intervals and the ratio of squared LF/HF coefficients calculated for each sample.
Results: See figure below.The values of LF/HF during routine recordings and before arrhythmic events were significantly different (* p<0.001 by ANOVA) except at two timepoints.

Conclusions: wavelet transform of HRV shows evidence of sympathovagal imbalance beginning over an hour before ventricular arrhythmic events, culminating just before arrhythmia onset.

P388 Correction of intraventricular asynchrony is the main mechanism by which cardiac efficiency improves by biventricular pacing in heart failure

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Biventricular pacing (BP) has been shown to improve mechanical efficiency and to reverse remodeling of the left ventricle (LV) in patients (pts) with refractory heart failure and wide QRS complex. Yet, among the pts with biventricular pacing, approximately 25% do not respond to the therapy despite a wide QRS complex.
Aim: To identify mechanisms responsible for a positive remodeling to BP in pts with severe heart failure and a wide QRS complex.
Methods: Twenty-one consecutive patients with refractory heart failure (NYHA 3.2±0.8) and wide QRS complex (179±28 ms) underwent echocardiography before, 3 days and 3 months after active BP. Intra- and interventricular asynchrony was quantified by tissue Doppler as a difference of activation times between basal segments of the LV (asynLV), and between left and right ventricular walls (asynLV-RV), respectively.
Results: Baseline heart rate, duration of AV interval and QRS complex, LV end-diastolic diameter, LV ejection fraction (LVEF), LV filling time and isovolumic contraction time did not correlate with the change of stroke volume (SV) or LVEF at 3 days or at three months. In contrast, a significant correlation was found between both baseline asynLV and asynLV-RV and the change of SV at 3 days (r=0.6, p<0.05, and r=0.54, ns) and at 3 months (r=0.88, p<0.01, and r=0.66, P<0.05). Also, the change of LVEF at 3 months correlated strongly with both baseline asynLV (r=0.75, p<0.01) and asynLV-RV (r=0.65, p<0.05). In addition, reduction of asynLV by BP inversely correlated with an increase in LVEF during follow-up (r=-0.66, p<0.05).
Conclusions: A reduction of intraventricular asynchrony is the main mechanism underlying an improvement of LV efficiency and reverse remodeling after BP. Conversely, a failure to reduce asynchrony predicts an unfavorable response during follow-up.

P389 Ventricular tachyarrhythmias during permanent pacemaker therapy – first results from the German multicenter EVENTS study

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Objectives: Ventricular tachyarrhythmias during permanent cardiac pacing have been reported casuistically in up to 20% of cases. Spontaneous incidence and potential interaction with cardiac pacing have become of increasing importance when newer pacing modalities (e.g. bi-ventricular pacing) are applied to patients with severe heart disease.
Methods: In a prospective multicenter trial (EVENTS) 227 consecutive patients eligible for permanent dual chamber pacing according to the ACC/AHA-Guidelines were included. No pts with overt ischemia, atrial fibrillation, or ICD indication were enrolled. Implanted pulse generators (PG; Pulsar, Discovery; GUIDANT Corp., Minneapolis), able to store 40 s of electrograms (EGMs) were programmed to trigger on ventricular tachyarrhythmias (4 cycles >120 bpm) closely to the MADIT criteria. Stored EGMs, histograms and counters were retrieved after 3, 9 and 15 months and systematically analyzed.
Results: During a mean follow-up (FU) of 12.8±4.9 months a total number of 3162 EGMs were documented and 2455 EGMs were finally further processed. 206 out of 227 pts had at least one FU, 145 pts were followed for 15 months. Of all analyzed EGMs ventricular tachyarrhythmias (at least 8 beats >120 bpm) occurred in 52 pts (25.2%), verified by stored EGM. VPBs and Lown IVa arrhythmia were documented in 4.5%. In 21 pts (10%) potential malignant forms of ventricular tachyarrhythmias occurred in more than one FU.
Conclusion: First data analysis revealed complex forms of ventricular tachyarrhythmias occurring in more than 25% of pts during permanent pacing within the first 15 months after implantation. The results may be of particular importance when complex pacing modalities are applied to pts with severe heart disease (e.g. bi-ventricular pacing). However, further data evaluation and studies using extended PG storage and capacity are needed to identify interaction and onset mechanisms of ventricular tachyarrhythmias and their prognostic significance during permanent pacing.

P390 Correlation of heart rate turbulence with other autonomic markers

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Background: The (cardiac) autonomic nervous system plays a decisive role in control and modulation functions at the origin of malignant arrhythmias. In the last years makers, which characterizes the autonomic state, became more and more important as risk stratifiers for post infarct mortality. A new marker of the autonomic nervous function is the Heart Rate Turbulence Slope (TS). Goal of this investigation was to examine the correlation of TS with other makers of the autonomous nervous system.
Method: 949 consecutive patients with acute myocardial infarction (AMI) take part in the study. Inclusion criterion was sinus rhythm and at least 1 VPC/24h. 90% of these patients were treated by PTCA and/or stenting during the acute phase of AMI. 91% received beta - blocker, 88% ACE Hemmer, 80% statins and 99% aspirin as adjuvant pharmacotherapy. In the second week after the AMI the following parameter were assessed: heart rate variability (HRV), TS, arrhythmia count, mean heart rate (mHR) and the left ventricular ejection fraction (LVEF).
Results: There were weak but significant correlations between the tested parameters (see table).

Correlation coefficients

	SDNN	mean HR	VPC/h	LVEF
TS	0.33; p<0.0001	-0.36; p<0.0001	-0.15; p<0.0001	0.26; p<0.0001
SDNN		-0.56; p<0.0001	-0.03; n. s.	0.28; p<0.0001
mean HR			0.08; p<0.01	-0.39; p<0.0001
VPC/h				-0.11; p<0.0001

Summary: The results shows significant correlations between TS and other markers of the autonomic control mechanisms.

ATRIAL FIBRILLATION: PACING AND TECHNICAL ASPECTS

P391 Prevalence and clinical characteristics of immediate reinitiation of atrial fibrillation after electrical cardioversion

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Objective: In patients with persistent atrial fibrillation (AF) sinus rhythm can be restored by electrical cardioversion(ECV). However, in about 10-20% of patients ECV has an unsuccessful outcome. An unsuccessful ECV outcome can be divided into two scenarios. First, ECV fails to restore sinus rhythm (total shock failure). Secondly, although sinus rhythm is restored, immediate reinitiation of AF (IRAF, recurrence within 2 minutes) occurs. Prevalence of shock failure and IRAF are unknown. However, this is of important since it has been established that patients with IRAF may eventually maintain sinus rhythm while patients with shock failure have a poor arrhythmia outcome.
Methods and Results: We evaluated ECV outcome in 482 consecutive patients and investigated which variables predicted the occurrence of either shock failure or IRAF. Shock failure occurred in 39 (8%) while IRAF occurred in 67 patients (14%). 131 patients had a first episode of persistent AF and were not treated with a class I or III anti-arrhythmic drug. Of these 131 patients 12 patients(9%) had an unsuccessful ECV due to shock failure, while 21 patients (16%) had IRAF. A longer duration of AF (8 versus 4 months, p=0.03) and the use of diuretics (58% versus 29%, p=0.05) predicted the occurrence of total shock failure while the use of ACE inhibitors (57% versus 33%, p<0.05) and a longer duration of AF (7 versus 4 months, p<0.01) were predictors of IRAF. There was a trend for a larger left atrium (49 versus 45 mm, p=0.1), a larger left ventricular end diastolic diameter (53 versus 50 mm, p=0.09) in patients with IRAF. Pretreatment with calcium channel blockers, digoxin and beta-blockers was not related to IRAF. Multivariate analysis revealed that a longer duration of AF was the only parameter predicting the occurrence of IRAF.
Conclusion: Unsuccessful ECV outcome is predominantly caused by IRAF. Both IRAF and shock failure occur more frequently if AF duration is longer.

P392 Does pace termination of atrial arrhythmias influence time of recurrence? Results of the European AT500 verification study

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Introduction: Prompt re-initiation of atrial fibrillation (AF) commonly occurs following electrical or chemical cardioversion. However, AF re-initiation following atrial anti-tachy pacing (ATP) is unknown. The purpose of this study was to compare the time to AF recurrence between episodes successfully terminated by ATP therapy (success), episodes spontaneously terminating after unsuccessful ATP (fail) and episodes spontaneously terminating without therapy (NoRx).
Methods: Data were obtained from 205 consecutive patients (3.2 ± 1.8 months of FU) implanted with the Medtronic AT500 (95% with AF history). We analyzed 2081 episodes from 109 patients meeting the following inclusion criteria: 1) stored EGM, 2) appropriately detected and terminated, 3) > 1 month post implant and, 4) available date and time of the next AF episode. To correct for multiple episodes, each patient's median time to AF re-initiation after success, fail and NoRx episodes was used for paired comparisons and data reports.
Results: Many of the patients (51/109) experienced a median time to AF re-initiation shorter than 5 min in all success, fail and NoRx episodes. There were no statistical differences in the median time to re-initiation among success, fail and NoRx episodes across patients.

	No Therapies(Rx)	success	fail
Number of episodes/pt, median (range)	0 (0-41)	2 (0-56)	5 (0-35)
Median time (minutes) to AF re-initiation/pt, median (range)	3.6 (0.3-7313)	1.6 (0.2-43494)	1.0 (0.2-26983)

Conclusion: AF re-initiation within a few minutes following successful ATP is common. These short re-initiation times do not depend on whether the AF episode was terminated by therapy or terminated spontaneously.

P393 Abnormal right atrial electrograms predict the development of chronic atrial fibrillation in paced patients with sick sinus syndrome

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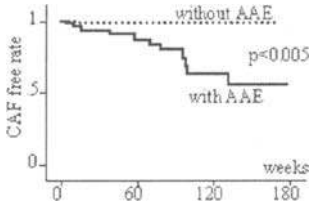
Although pacing therapy for sick sinus syndrome (SSS) is established, subsequent development of chronic atrial fibrillation (CAF) makes pacing therapy not feasible in some patients. The aim of this study was to evaluate whether electrophysiologic characteristics of atrial muscle can predict the development of CAF after pacemaker implantation in patients with SSS.

Methods: Eighty-nine patients with SSS underwent electrophysiologic study (EPS) before pacing therapy. In EPS, catheter mapping of 12 sites (four aspects of the high, middle, and low right atrium) was performed during sinus rhythm. An abnormal atrial electrogram (AAE) was defined as having a duration of 100 ms or longer or eight or more fragmented deflections or both. Right atrial extrastimulation was also performed for atrial vulnerability.

Results: During follow-up for 85 ± 50 months, development of CAF was observed in 12 patients (group A). The remaining 77 patients remained in sinus rhythm (group B). The number of AAE was significantly grater in the group A than in the group B (2.7 ± 2.3 vs 0.8 ± 1.2; $p<0.001$). The distribution of AAE was also greater in the group A; patients in the group A had a greater number of AAE than patients in the group B in both high and middle right atrium ($p<0.005$ and $p<0.01$, respectively). Figure shows the CAF free curve according to Kaplan-Meier analysis. Almost 50% of the paced patients with AAE (n=42) in high and/or middle right atrium developed CAF after 15 year, whereas only 2% of the paced patients without AAE (n=47) developed CAF ($p<0.005$). Indices of atrial vulnerability did not influence the transition to CAF.



CAF free rate.

Conclusion: Our data suggest that the existence of AAE in high and/or middle right atrium is predictive of the development of CAF in paced patients with SSS.

P394 High-rate overdrive pacing for prevention of immediate reinitiation of atrial tachyarrhythmias: results from a prospective randomized trial

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In patients (pts) with atrial tachyarrhythmias (ATs), immediate reinitiation of AT (IRAT) can be responsible for the progression of atrial electrical disease. Atrial overdrive pacing at a high rate after restoration of sinus rhythm may be able to suppress IRAT. This hypothesis was examined in a prospective, randomized, single-blind cross-over trial.

Methods: In pts with pacing indication and AT, a DDDRP system (AT500, Medtronic Inc.) was implanted. Atrial preventive and antitachycardia pacing (ATP) was deactivated during the first month after implantation. Thereafter, devices were interrogated and pts with stored AT episodes and reliable AT detection were randomized to receive either post mode switching overdrive pacing (PMOP) at 120 bpm for 2 min or no PMOP after spontaneous or paced termination of the AT. Atrial ATP and 2 other preventive pacing algorithms (atrial rate stabilization, atrial pacing preference) were activated. After another 3 months, pacemaker memory functions (stored AT episodes with atrial electrograms, AT burden) were interrogated, and quality of life and AT related symptoms were assessed using questionnaires (SF-36, symptom checklist). Pts were then crossed over for a second 3 month period. Stored AT episodes were manually reassessed for reliability of AT detection. Primary study endpoint was the time that the pts were in AT (AT burden in %) with vs without PMOP active (intention to treat analysis). A secondary endpoint referred to the number of pts in whom AT burden was reduced with PMOP.

Results: 30 pts with AT episodes and reliable AT detection were enrolled and completed both study periods. Two early cross-overs occurred (1 pt from PMOP 120 bpm to no PMOP, 1 pt the alternative) due to symptoms. Mean AT burden (11 ± 21 vs 11 ± 19%), quality of life and AT related symptoms were not different with or without PMOP. AT burden was reduced with PMOP in 12 pts, unchanged in 6 pts, and increased in 12 pts.

Conclusions: In this study, overdrive pacing at 120 bpm for 2 min after spontaneous or ATP induced termination of AT did not change the AT burden. Further studies are necessary to identify a subset of pts who may benefit from this therapy.

P395 Impact of left ventricular function on atrial antitachycardia pacing efficacy: AT500 Italian registry

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Introduction: The AT500 Italian Registry enrolled at present time 330 patients (pts) with frequent episodes of paroxysmal atrial fibrillation (AF) implanted with a Medtronic AT500™ pacemaker (mean age 71 ± 9 years; mean follow-up 6.3 ± 4.9 months).

Aim of the study: To assess how left ventricular ejection fraction (LVEF) may influence the efficacy of atrial antitachypacing therapies (ATP) delivered to treat atrial tachyarrhythmias.

Results: ATP efficacy in treating AF and atrial tachycardia (AT) episodes (as classified by the device) is reported in the following Table.

We considered 1238 episodes recorded in 37 pts with known left ventricular ejection fraction (LVEF)(19 M, 18 F - mean age 70 years).

ATP efficacy in the two groups of pts

	LVEF<55%	LVEF≥55%	
	10 pts	27 pts	
Total	124/350	93/878	p<0.005
	35.4%	44.8%	
AF	50/163	74/289	p = ns
	30.7%	25.6%	
AT	74/187	319/589	p<0.0001
	39.6%	54.2%	

Conclusion: Our data show that a preserved left ventricular ejection fraction is associated with an higher efficacy of atrial antitachycardia pacing, especially when treating slower and/or more organized atrial tachyarrhythmia episodes. These data are of clinical relevance with regard to device and hybrid treatment of atrial fibrillation associated with left ventricular dysfunction or congestive heart failure.

P396 Patients with atrial tachyarrhythmias have multiple onset patterns: implications for pacing for prevention of atrial tachyarrhythmias

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Atrial pacing is being studied for its potential to prevent atrial tachyarrhythmias (ATs). To tailor optimal AT prevention pacing algorithms to an individual patient (pt), knowledge about AT onset patterns may be helpful.

Methods: Pts with a pacing indication and ATs received a DDDRP system (AT500, Medtronic Inc) with dedicated memory functions for storage of AT episodes including an atrial electrogram and marker annotation for 48 events before AT onset. Memory functions were activated after implantation and devices were interrogated before hospital discharge and 1 month after implantation. During this time period, all preventive pacing algorithms and antitachycardia pacing were deactivated. AT episodes were printed out, the reliability of atrial sensing was manually assessed and all AT episodes with atrial under- or oversensing were excluded. For the following prospectively defined onset patterns, the incidence was calculated: 1. immediate (< 1min) reinitiation of AT, 2. supraventricular (SV) run before AT, 3. SV bigeminus, 4. SV trigeminus, 5. > 3 isolated atrial premature beats (APBs), 6. continuous atrial rate increase, 7. continuous atrial rate decrease, 8. > 3 ventricular premature beats, 9. alternating atrial pacing and sensing, 10. regular intrinsic atrial activity, 11. regular atrial pacing, 12. no pattern. Primary endpoint of this study was the number of pts with > 1 onset pattern, secondary endpoint was the relative incidence of each onset pattern in all episodes.

Results: In 65 of 90 pts enrolled into the study, 1430 AT episodes were stored. 844 AT episodes were excluded due to atrial sensing errors; of the remaining 586 AT episodes, immediate AT reinitiation was found in 217 (37%), regular atrial pacing in 165 (28%), SV runs in 118 (20%), SV bigeminus in 114 (19%), regular atrial sensing in 53 (9%), SV trigeminus in 27 (5%). APB related onset patterns were found in 276 (47%) episodes, short-long sequences in 192 episodes (33%). Eight pts had only 1 AT onset patterns, the remaining 32 pts had 2-8 (mean 3.5 ± 1.8) onset patterns.

Conclusions: The majority of pts with ATs have multiple onset patterns. While immediate AT reinitiation and APB related onset patterns are frequent, also a high percentage of AT episodes start from regular atrial pacing or sensing.

P397 Does left atrial size modify response to pacing algorithms dedicated to prevent atrial fibrillation?

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Background: Although standard atrial pacing seems to prevent atrial fibrillation (AF) recurrences in some pts with documented paroxysmal (P) AF, further beneficial effects of additional pacing algorithms (alg) remain controversial. We sought to determine left atrial (LA) size influence on pts response to these pacing alg.

Methods: Pts with PAF (at least 3 episodes during the last year) were included in a multicentre, randomized, cross-over study (6 months each). They were implanted with a DDD pacemaker (chorum 7334, ELA, Montrouge, France) and after one month, randomly assigned to DDD pacing at 70 bpm with (DDD+alg) or without alg (DDD). Three different alg were used: Sinus Rhythm Overdrive (permanent atrial pacing just above the sinus rate), Post-Extrasystolic Pause Suppression (controls cycle length variation after premature atrial contraction, PAC) and Acceleration on PAC's (increases temporarily pacing rate upon frequent PAC's). Study end points were recurrences (number and duration) of PAF detected by pacemaker during both pacing modes. LA diameter was measured at inclusion by M-mode echocardiography.

Results: The study group included 59 pts (mean age 68 ± 10 years; 36 M). Median LA diameter (40 mm) was used as a cut-off value to separate pts into 2 subgroups LA < 40 mm (27 pts; LA diameter 34.7 ± 3.6 mm) or > or = 40 mm(32 pts; LA diameter 44.5 ± 4.1 mm, p<0.0001). Results are summarized in the table.

	LA < 40 mm		LA > or = 40 mm	
Pacing mode	DDD	DDD + alg	DDD	DDD + alg
AF duration (days)	12.7 ± 37.3	12 ± 29.4 (NS)	16.6 ± 32.6	13.3 ± 30.8 *
Number of AF episodes	111.6 ± 271.5	105 ± 227.9 (NS)	113.4 ± 173.9	86.1 ± 148.3 *

* p<0.05

Conclusion: Additional algorithms to standard DDD pacing seem to be more effective to reduce PAF recurrences (length and number of episodes) in pts with dilated LA. This result could be explained by a higher vulnerability to PAC of this group of pts leading to a higher protection of the studied algorithms.

P398 Advanced pacemaker diagnostic features in the identification of "substrate fibrillators": relevance for AF preventive pacing algorithms

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Pacing algorithms to prevent paroxysmal atrial fibrillation (AF) are mainly based on the suppression of premature atrial contractions (PAC's) which are supposed to play a major role in the initiation of AF. For the specific use of the various offered algorithms a detailed characterisation of the AF episodes was performed by analysis of the pacemaker (PM) arrhythmia diagnostic features according to the PAC activity before AF onset.

Methods: 49 patients (67 ± 11 years) with dual chamber pacing (Vitatron, "Selection" Series) and a history of paroxysmal AF were included. After a mean follow-up of 94 ± 25 d the following PM diagnostic parameters were studied: (1) number of PAC's/hr during sinus rhythm, (2) total AF burden (% of storage period), (3) AF episode duration, (4) number of AF episodes/d, (5) frequency of PAC's/min during the last 5 min before AF onset, (6) percentage of atrial pacing. According to the frequency of PAC's/min during the last 5 min before AF onset the patients were divided into Group A with "few PAC's before AF onset" (>70% of the episodes preceded by <2 PAC's/min, n=23) and Group B with "frequent PAC's before AF onset" (<70% of the episodes preceded by <2 PAC's/min, n=26).

Results: Group A patients presented significant smaller numbers of PAC's/hr overall (10.9 ± 12.8 vs. 93.7 ± 172.7, p<0.05), significant higher total AF burden (14.3 ± 17.8% vs. 7.6 ± 13.5%, p<0.05) and significant higher numbers of "long" AF episodes >1 hr (29.9 ± 27.6% vs. 12.8 ± 17.8%, p<0.01). The number of AF episodes/d did not differ significantly between both groups (2.8 ± 4.7 vs. 1.9 ± 2.7, p=0.22) as not the frequency of atrial pacing (52.4 ± 34.9% vs. 61,5 ± 30.5%, p=0.41).

Conclusions: 1. Patients with few PAC's during the last 5 minutes before AF onset demonstrated to have a higher AF burden compared to patients with a high PAC activity. 2. The elevated AF burden in these patients is due to longer AF episodes. 3. This coincidence of few or missing PAC activity before AF onset ("sudden onset"), increased AF burden and longer episode duration may be the consequence of a higher atrial "substrate factor". 4. Depending on the AF onset characteristics a differential programming of AF preventive pacing algorithms may be necessary for effective electrical AF prevention.

P399 Chronic single-site interatrial septal pacing prevents paroxysms of atrial fibrillation and reduces atrial wall stretch

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Objective: to evaluate effects of chronic single-site interatrial septal pacing on intraatrial conduction, haemodynamics and assess its potential to prevent paroxysms of atrial fibrillation in patients with sick sinus syndrome (SSS).

Methods: Thirty five consecutive patients with SSS underwent electrophysiological study and received single-chamber pacemaker for chronic AAI pacing. In 22 patients (68±8 years) with history of SSS and weekly symptomatic paroxysms of atrial fibrillation (PAF group), the active-fixation atrial lead was positioned at the posterior interatrial septum (IAS). The other 13 patients (67±9 years) had SSS only (SSS group) and the atrial lead was placed in the right atrial appendage (RAA). All patients underwent transthoracic echocardiography. All patients have been followed up for up to 36 months for assessment of PAF recurrence.

Results: 1) P-wave duration during sinus rhythm at baseline was not different between the PAF and SSS groups. IAS pacing shortened P-wave duration (105±16 ms vs. 92±18 ms, p<0.05), while RAA pacing increased P-wave duration (100±19 ms vs. 116±18 ms, p<0.01). 2) Baseline cardiac haemodynamics assessed by EchoCG was not different between the groups. Left atrial volume index (LAVI) was decreased during IAS pacing in PAF patients (45±12 vs. 32±11 ml/m^2, p<0.05, for measurements at baseline and during pacing respectively), while RAA pacing did not affect that. 3) During the follow-up period (17±11 months), 17 of 22 PAF patients were free from recurrence of arrhythmia paroxysms. None of SSS patients had PAF during the follow-up period.

Conclusion: 1) Our findings suggest that IAS pacing facilitates atrial conduction as it shortens P-waves while RAA pacing tends to prolong them. 2) Prevention of PAF by chronic IAS pacing in patients with SSS shown in our study may be explained not only by enhanced atrial synchronism but also by modification of other proarrhythmic factor such as atrial wall stretch as demonstrated by reduction of LAVI during the pacing.

P400 Autocapture enhancements: (1) unipolar and bipolar lead compatibility and (2) bipolar pacing capability on bipolar leads

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Beat-by-beat AutoCapture (AC) maximizes device longevity by minimizing stimulus amplitude while assuring patient safety. Currently, AC permits use of only bipolar leads. We have now devised a detection method that operates on unipolar and bipolar leads and covers all pacing and sensing combinations (but bipolar pace and sense at the same time). A new detection method for unipolar sensing uses the integral of the negative portion of the unipolar evoked response (UVERI) as a robust capture detection feature. When using bipolar leads, the new method provides the flexibility of bipolar or unipolar pacing. Unipolar ventricular IEGM signals were collected from 71 patients age 73.7 ±9.9 years; 9 with high polarization (POL) leads, 62 with low POL leads. High POL leads have polished platinum or activated carbon electrodes. Low POL leads had TiN, platinized platinum, or IrOx electrodes. The IEGMs were recorded 544 ±796 days after implant. Affinity pacemakers (St. Jude Medical, Sylmar, USA) performed an automatic capture threshold test while the IEGM signals were recorded in a 3500 or 3510 programmer (St. Jude Medical, Sylmar, USA). These digitized signals were saved for off-line analysis. We calculated the UVERI at up to six (depending on capture threshold) pacing voltages and the POL integral at 4.5 volts and at loss of capture. An automatic calibration algorithm determined whether signal to noise was adequate for AC operation. AC is possible with 60/62 of the low polarization leads. While AC operation was possible with 6/9 of the high polarization leads. The average values from the data collected are: average UVERI is -4.1 ±2.1 mV; average peak negative voltage is -10. ±3.7 mV; average POL is 0.3 ±0.34 mV; and average signal to noise (UVERI/POL) is 38 ±71. In all cases the algorithm correctly determined feasibility of using AC with the lead electrodes tested and, if so, what UVERI threshold should be used.

P401 Testing a new single lead for left atrial and left ventricular-based DDD pacing in an animal experiment

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Background: Biventricular and left ventricular pacing was reported to improve hemodynamics, physical capacity, and quality of life in patients with congestive heart failure. A recently developed left-sided, single-pass pacing lead has the advantage of reducing the number of implanted electrodes to only one lead with the capability of left atrial- and left ventricular-based VDD/ DDD pacing (LSDL – Left-Sided Single-Pass DDD Lead).
Methods: To test the feasibility and pacing characteristics the LSDL was implanted in four pigs (two acute, two acute/chronic; weight 60 ± 11 kg). The pigs were chosen because of their anatomic similarities to human hearts. After inserting the introducer set (SCOUT, Biotronik) under fluoroscopy via the jugular vein and into the coronary sinus, an angiogram was recorded to select one of three LSDL types (atrio-ventricular pole distance: 6.5, 9.0, or 11.5 cm). After introducing the LSDL and taking the intra-operative (acute) measurement, a dual-chamber pacemaker was implanted.
Results: The time for lead insertion was 40 ± 33 min with 2.3 ± 2.9 repositions. Recorded amplitudes were for P-waves 2.1 ± 0.1 mV and for R-waves 8.5 ± 2.1 mV, left atrial and left ventricular pacing thresholds were 2.6 ± 0.3 V and 1.2 ± 0.6 V at 0.5 msec, respectively and the atrial and ventricular impedances were 244 ± 27 Ohm and 691 + 232 Ohm, respectively. Chronic measurements were performed every other day over a two-week period; pacing and sensing values were constant. No far-field R-wave sensing in the left atrium and no safety window pacing (indicating ventricular cross talk sensing) was observed.
Conclusion: These data show, that the LSDL has good implantation handling and acceptable pacing and sensing characteristics. As a result, patients with congestive heart failure could profit from the LSDL, suggesting that the hemodynamic benefit of this one lead configuration is similar to conventional biventricular pacing, using a three lead system. The LSDL is currently being tested in humans in an ongoing feasibility study (Corox SL Pilot Trial).

P402 Does the availability of multiple left heart lead and delivery systems matter for cardiac resynchronization therapy?

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Background: Cardiac resynchronization therapy has been shown to improve quality of life and functional capacity in a subset of heart failure patients. Improvements in implant time and success rate are being pursued. We evaluated the impact of having multiple left-heart (LH) lead and delivery system (DS) options on implant time and success rate with the belief that multiple designs are needed to access the Coronary Sinus (CS) and fixate the lead in the various patient anatomies.
Methods: In the MIRACLE trial, investigators chose from using a 6 Fr unipolar lead (2187) or a 6 Fr bipolar lead (2188). During this study, a DS (6216) was used to cannulate the CS providing a pathway to the cardiac veins. The DS included a Modified MB1 or MB2 curved guide catheter to achieve CS cannulation. In the InSync III trial, investigators chose from using the same leads (2187/2188) or a new 4 Fr over-the-wire design (4193). This lead can be placed in the cardiac veins using a standard pacing stylet or an interventional guide wire (.014"-.018"). A new DS (6218) was also provided as a second option in the InSync III trial. The new DS included a longer soft-tipped catheter with a straight distal end for deeper CS engagement. This DS is inserted into the CS using a steerable or fixed shape EP catheter.
Results: Implant success rates and median procedure times with interquartile (IQ) ranges (25%-75%) are compared below in table 1.

Table 1: Success Rate and Implant Times

	Implant Success Rate		Time to Engage CS (min)		Time to Place LV Lead (min)		Total Operative Time (min)	
	N	Rate	Median	IQ Range	Median	IQ Range	Median	IQ Range
MIRACLE	528/571	92.5%	11	5-22	29	17-59	162	123-216
InSync III	253/264	95.8%	7	3-14	10	5-20	131	98-180
p-value	p=0.078		p<0.0001		p<0.0001		p<0.0001	

P-values calculated using t-test (implant times) and chi square (success rate) analysis.

Conclusions: These data support our belief that the availability of multiple LH lead designs and DS options are associated with a trend toward a higher success rate and significantly reduced median implant times. Current technology has shown a 95.8% implant success rate with a mean operative time of 131 minutes.

P403 High versus normal impedance leads: impact on pacemaker generator longevity

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Background: Pacemaker generator longevity correlates negatively to current consumption and positively to the resistance of the pacing lead. Therefore, the use of a high impedance pacing lead theoretically results in an extension of generator longevity due to the high pacing impedance and the consecutive reduction of the charge transfer from the battery through the electrode-tissue interface. In this prospective, randomized trial the effect of high versus normal impedance ventricular leads on generator longevity was studied.
Methods: Twenty-six pts were included in this study (11 male, 15 female, age 73±13 years). A normal impedance lead (SJM model 1452t, bipolar) was implanted in 13 pts, the remaining pts received a high impedance lead (Medtronic model CapSure Z 5034 bipolar) in a randomized fashion. In order to create almost identical pacing conditions, all pts received a Medtronic Kappa KDR pacemaker and the same atrial lead model (Medtronic model 5068).
Results: After a mean follow up of 36.6±4.3 (Medtronic 5034) and 33.5±4.9 months (SJM 1452) no significant differences were observed in pacing and sensing thresholds in both groups. There were no significant differences in atrial lead performance as well as in lead related complications in both groups. The mean impedance of the high impedance pacing leads (5034) was 875.7±299.2 Ohms as compared to 631.5±152.5 Ohms for the standard pacing leads ($p < 0.001$). The longevity of the generator was calculated automatically by a programmed pacemaker algorithm. The 5034 leads provided a significant increase in generator longevity of 104.6 ±8.9 months vs. 98.0±7.7 months as compared to 1452 leads (p=0.028). This means an increase in longevity of 6.6 months in the high impedance lead group.

longevity (months)	maximum	minimum	mean
5032 lead	115.2±10.1	94.6±8.1	104.6±8.9
1452 lead	108.0±8.5	88.8±6.8	98.0±7.7
difference (months)	7.2±1.6	5.9±1.3	6.6±1.2
p-value (t-test)	0.023	0.042	0.028

Conclusion: Implantation of a high impedance lead for ventricular pacing results in a clinically relevant extension of generator longevity.

P404 Results of a randomized study comparing two atrial lead implantation sites: right atrial appendix versus lateral wall

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Aim of this prospective randomized study was to evaluate the impact of the atrial lead implantation site on the subsequent development of atrial fibrillation. Patients (pts) with an indication for a dual chamber pacemaker without a history of atrial fibrillation were included. Pts were randomized either for atrial lead implantation at the right atrial lateral wall (RALW) vs implantation in right atrial appendix (RAA). Primary endpoint was the new development of atrial fibrillation during follow up.
Results: Dual chamber pacemakers were implanted in 99 pts. The indication was AV-block in 48 pts, sick-sinus syndrome in 51 pts. No pt had a history of atrial fibrillation before implantation. At the time of implantation 49 pts (67 ± 12 years) were randomized to the RAA, 50 pts (66 ± 12 years) were randomized to RALW. There was no significant differences either in demographic datas, clinical parameters and the indication of dual chamber pacemaker. Mean follow-up duration was 484 ± 358 days. In 28/99 pts (28%) atrial fibrillation was documented. In the Kaplan-Meier analysis the probability for the occurrence of atrial fibrillation during the initial 3 years was 29% in pts after lead implantation in the RALW and 54% in pts after implantation in the RAA ($p = 0.08$).

Atrial lead implantation site	Atrial fibrillation	No atrial fibrillation
RAA (49 pts)	17 pts (35%)	32 pts (65%)
RALW (50 pts)	11 pts (22%)*	39 pts (78%)

* $p = 0.16$

Conclusion: New onset of atrial fibrillation was observed in 1/3 of pts after lead implantation in the RAA vs 1/5 of pts after atrial lead implantation at the RALW ($p = 0.16$). In the Kaplan-Meier analysis a tendency was observed that pts after lead implantation in the RAA had earlier and more often episodes of atrial fibrillation during follow-up compared to pts with implantation at the RALW.

INFLAMMATORY INJURY OF THE VESSEL WALL

P405 Soluble VEGF and its soluble receptor, sFLT-1, and their correlation to endothelial-dependent vasodilation

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Elevated concentrations of sVEGF are found in certain diseases with endothelial dysfunction. Similar VEGF concentrations were measured in healthy smokers (S) and controls (C). sFLT-1 has a high affinity for VEGF and may function as antagonist to VEGF. We were interested in the correlation between VEGF, sFlt-1 and endothelial function in healthy S and C.
In 20 healthy smokers and 20 matched control subjects without further cardiovascular risk factors, VEGF and free FLT-1 were measured from citrate plasma with an ELISA. Flow- (FMD) and acetylcholine-mediated (AMD) vasodilation (endothelial-dependent) (EDV) and nitroglycerine-mediated (NMD) vasodilation were measured on lower extremities with plethysmography (ml/100 ml tissue/min).
AMD was lower in S compared to C (11 vs. 15 ml/100 ml tissue/min ($p < 0,05$)). FMD (11 vs. 14) and NMD (3,5 vs. 4,4) showed only a trend. S and C showed similar VEGF-concentrations (12,9 ± 5,9 and 14,9 ± 11,8 pg/ml). sFLT-1 was lower in S than in C (33,9 ± 5,9 vs. 47,1 ± 34,0 ng/ml, $p < 0,01$), without a correlation between pack-years and FLT-1. There was no correlation between VEGF and sFlt-1 levels. An inverse correlation was found in both groups between VEGF and AMD (S: r= - 0,6, $p < 0,01$, C: r= -0,71, $p < 0,005$) and FMD (S: r= -0,56, $p < 0,05$, C: r= -0,58, $p < 0,005$), but not NMD. S and C with higher AMD (>12 ml/100 ml tissue/min) showed lower plasma VEGF ($p < 0,001$).
Healthy smokers showed impaired EDV. The soluble VEGF receptor, sFlt-1 is lower in smokers without showing a correlation to EDV. No correlation between FLT-1 and VEGF was found in these subjects. The amount of plasma sFlt-1 greatly exceeds VEGF. Longstanding smoking did not show an effect on VEGF concentrations. Circulating VEGF correlates inversely with EDV in smokers and controls, sFLT-1 seems not to play a dominant regulatory role in this context.

P406 Intraplaque C-Reactive protein is associated with plaque vulnerability

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Background: The acute phase protein C-reactive protein (CRP) is an important risk factor for coronary artery disease. Preliminary data showed that CRP also accumulates in coronary plaques and promotes foam cell formation and/or complement activation that may lead to unstable coronary plaques.
Aim of the study:
To investigate the relation between CRP off culprit coronary atherectomy specimen and the expression of coronary syndromes.
Methods: A total of 54 patients with stable (SA, n=21) and unstable (UA, n=15) angina and acute myocardial infarction (MI, n=18) underwent directional coronary atherectomy (DCA) for culprit lesions. Cryostat sections of atherosclerotic plaques were immunohistochemically stained with the monoclonal antibodies CD-68 (macrophages; MAC), 5G4 (CRP), aE11 (complement, C5b-9) and 12E7 (Ox-LDL). Qualitative examination was performed by determination of the immunopositive areas in relation to fibrous cap, atheroma and colocalization. Quantitative analysis was performed by using image cytometry (QPRODIT 5.2) with systematic random sampling (expressed as percentage immunopositive tissue area of the total tissue area).
Results: Colocalization of CRP and complement was observed in the fibrous cap and atheroma and was more frequently present in plaque specimen of patients with MI (100%) compared to patients with SA (75%, p=0.079). Moreover, colocalization of CRP with Ox-LDL was significantly more frequently present in MI (100%) compared to SA (47%, p=0.0016). The table below shows the quantitative relation between CRP and MAC in relation to SA, UA and MI.

	SA (n=21)	UA (n=15)	MI (n=18)
MAC**	20±10	30+/13*	44±12*#
CRP**	12±9	25±16*	24±14*

**percentage immunopositive tissue area/total tissue area*p< 0.01 compared to SA and #p<0.01 compared to UA (ANOVA).

Conclusions: Amounts of CRP in culprit coronary lesions increase with the severity of acute coronary syndromes. Colocalization of CRP, complement, ox-LDL and macrophages suggests a pathogenic role for CRP in plaque destabilization.

P407 Increased levels of the furin, membrane type-1 metalloproteinase and metalloproteinase 2 activation cascade after balloon dilation

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Background: Matrix Metalloproteinase (MMP) activation is an important event in cardiovascular diseases such as de novo atherosclerosis, restenosis after balloon angioplasty and during sustained flow changes. Inhibition of MMPs, which are the only enzymes capable of degrading collagen, results in diminished arterial remodeling. Understanding the activation cascades of the MMPs might result in the development of more specific inhibitors. MMP-2, one member of this family, is activated by membrane type-1 MMP (MT1-MMP) that is activated by Furin, a proprotein convertase. Recently, we described the existence of the Furin, MT1-MMP and MMP-2 activation cascade in the arterial wall after sustained flow changes (physiological). Now we studied this activation cascade after pathological arterial injury (balloon dilation).
Methods: Unilateral balloon dilation was performed in femoral and iliac arteries in 25 New Zealand White rabbits. Arteries were harvested after 2, 7, 14 and 28 days. Diameter changes and intimal hyperplasia were determined compared to post-dilatation as a percentage of the total vessel area. Furin and MT1-MMP mRNA expression were determined by quantitative-PCR, MT1-MMP protein levels by western blotting and MMP-2 activation by zymography. Contralateral arteries were used as controls.
Results: see table

Expression levels

Days of survival	2	7	14	28
Diameter change (%)	3.8 ± 2.4	-8.3 ± 11.0	-9.0 ± 4.6	-9.7 ± 7.8
Intimal hyperplasia (%)	0	1.5 ± 0.6	5.0 ± 1.3	16.7 ± 2.7
Furin mRNA	9.5 ± 4.7 *	5.9 ± 3.2 *	3.1 ± 1.0	5.6 ± 2.7
MT1-MMP mRNA	6.8 ± 3.9	3.3 ± 0.7 *	7.9 ± 2.3 *	5.2 ± 1.7 *
MT1-MMP protein	1.6 ± 0.3	3.1 ± 0.7 *	16.9 ± 8.0 *	25.1 ± 11.0
active MMP-2 protein	17.2 ± 5.9 *	65.2 ± 23.7 *	124.9 ± 38.2 *	40.0 ± 20.2 *

Ratio operated/control for expression levels; mean ± sem, * =p<0.05

Conclusions: Increase in arterial Furin and MT1-MMP expression preceded or coincided with increased MMP-2 activation after balloon dilation. This study confirmed the presence of a proprotein convertase- metalloproteinase axis in the artery and opens the use of Furin inhibitors to prevent arterial remodeling and neointima formation after injury at the root of activation.

P408 Synthesis of the interleukin-6 receptor in human PMN is regulated post-transcriptionally via the mTOR signaling pathway

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Polymorphonuclear leukocytes (PMN) adhesion and migration are involved in host defense and serve a beneficial role in a well-contained inflammatory response. However, in dysregulated inflammation, PMN may contribute to myocardial tissue damage (i.e. myocardial infarction). The cytokine Interleukin-6 and its receptor (IL-6R) are considerably involved in this inflammatory scenario. Although these mechanisms are complex, it is generally believed that the majority of tissue damage results from the release of preformed mediators. To date, it is not known, if PMN have regulated protein synthesis at the transcriptional level. We isolated PMN from healthy donors and activated them with platelet activating factor (PAF) [1nM-1μM] for 1-60 min.. Gene array analysis revealed that PMN contain multiple mRNAs, but PMN-activation with PAF does not induce a broad transcriptional response. Therefore, we concluded that PMN bypass well-known transcriptional regulatory pathways in favor of direct translation of preexisting mRNAs into protein. The mTOR (mammalian target of rapamycin) translational pathway is activated in PMN that were stimulated by PAF. By western blot analysis, we were able to show, that p70S6 kinase, a downstream kinase of mTOR, and 4E-BP1 are phosphorylated within one minute. The phosphorylation of p70S6 kinase and 4E-BP-1 were completely inhibited by rapamycin [10nM] indicating that mTOR is a crucial upstream signaling component of this translational pathway in PMN. By PCR, sequencing and western blot analysis we confirmed that mTOR1 is the predominant homologue present in PMN. Using S35-methionine incorporation and 2-dimensional gel electrophoresis, we also found that PMN synthesize multiple proteins upon activation with PAF [10nM]. The synthesis of some proteins was suppressed by rapamycin, while actinomycin D had minimal effect. We identified one of these proteins as the IL-6R. Further studies demonstrated that IL-6R transcripts are constitutively present in resting PMNs and the 5'-untranslated region of this mRNA has complex secondary structure and multiple polypyrimidine tracts making it an excellent candidate for mTOR-dependent translation. By western blot analysis we demonstrated, that the IL-6R is rapidly (within 30 min) synthesized in PMN. Rapamycin completely abrogated this response while actinomycin D had no influence, indicating again that the production of the IL-6R in PMN is translationally regulated. Taken together, these data demonstrate that PMN synthesize biologically relevant proteins - among these the IL-6R - through translationally driven mechanisms.

P409 Effects of vitamins C and E on serum levels of leukocytes adhesion molecules and lipid hydroperoxides, in chronic smokers

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Background: Serum levels of soluble vascular cell adhesion molecule (sVCAM-1) and soluble intercellular adhesion molecule (sICAM-1), as well as lipid hydroperoxides (LPO) (marker of lipid peroxidation), are implicated in the pathogenesis of atherosclerosis. Purpose of this study was to investigate the effect of combined administration of antioxidant vitamins C and E on endothelial function, and serum levels of sICAM-1, sVCAM-1 and LPO, in chronic smokers.

Methods: 36 healthy young smokers (20 males 16 females aged 36±2 years) were enrolled in this double blind placebo controlled study. Subjects were divided into 4 groups receiving vitamin C 2g/day (n=10) (group A), vitamin C 2g/day and vitamin E 400IU/day (n=11) (group B), vitamin C 2g/day and vitamin E 800IU/day (n=9) (group C) or placebo (n=6) (group D), for 4 weeks. Forearm blood flow was measured using venous occlusion strain gauge plethysmography. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to post reactive hyperemia blood flow. Endothelium independent % change flow (NTR%) was assessed after sublingual nitroglycerin administration. Plasma levels of sVCAM1, and sICAM1 were determined by enzyme linked immunosorbent assay, while LPO was determined using a spectrophotometric assay.

Results: Blood pressure, heart rate, body weight, basal forearm blood flow and NTR% were similar before and after treatment. FMD was significantly increased in groups B (46.6±5.5 to 74.1±9.3%, $p<0.05$) and C (43.6±3.9 to 74.9±4.2%, $p<0.01$), while remained unaffected in groups A and D. Serum levels of sVCAM-1 and sICAM-1 significantly reduced in group C (from 339±14 and 318±21 to 298±11 and 250±19 ng/ml respectively, $p<0.05$ for both), while remained unaffected in groups A, B and D. LPO was significantly reduced in groups B and C (from 14.5±1.2 and 15.4±2.9 to 8.8±1.6 and 8.3±1.7 iM respectively, $p<0.05$ for both).

Conclusions: Chronic administration of vitamin C (2g/day) combined with vitamin E (800IU/day), reduces blood levels of sVCAM-1 and sICAM-1, improves endothelial function and reduces lipid peroxidation in healthy young smokers. These findings may have therapeutic implications in chronic smokers.

P410 Signal pathways of integrin-rac-p38MAPK mediate p53-dependent SMC apopotsis

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Apoptosis of smooth muscle cells (SMCs) caused by biomechanical force represents one of the first events in the pathogenesis of ateriosclerosis (Xu Q, Trands Cardiovasc. Med. 2000;10:35-41). To investigate signal transduction pathways leading to apoptosis, SMCs growing on flexible membranes precoated with collagen I, laminin, elastin, and pronectin® were subjected to cyclic strain stress. Increased SMC apoptosis was 5.7 fold higher on collagen I matrix-coated plates compared to other matrices. Such increased apoptosis was blocked by pretreatment with either cytochalasin B, a toxin inhiniting integrin signaling, or with an anti-beta1 integrin monoclonal antibody. Only SMCs grown on collagen I showed a significant increase in p53 protein production. Gel mobility shift assays revealed that mechanical stress rapidly led to p53 activation, which was largely attenuated by SB202190 (p38MAPK inhibitor) pretreatment, or dominant negative Rac transfection. Kinase assays demonstrated that p38MAPK directly phosphorylates p53. SMCs derived from p53-/- mice lacking p53-binding activity lost its ability to express Bax and showed no apoptosis by strain stress. Likewise, mechanical stress resulted in upregulation of anti-apoptotic Bcl-2 and Bcl-xL, and a marked loss of mitochondrial membrane potential occurred. Furthermore, when integrin receptors were block p38MAPK activation and p53 phosphorylation were significantly inhibited in stressed SMCs. Taken together, our data provide the first evidence that p53 activation and Bcl-2 family protein expression play a crucial role in SMC apoptosis induced by mechanical stress, during which mitochondria are key regulators, while integrin-rac-p38MAPK pathways contribute to p53 activation.

P411 Role of caveolin in mechanic stretch induced proliferation of vascular smooth muscle cells

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Backrgound: Increased mechanic forces as ocuring in severe hypertension or venous bypass grafts cause increased proliferation of vascular smooth muscle cells (VSMC) which represents a major component in vascular lesion formation. The Phosphoinositide 3-kinase (PI3K)/proteinkinase B (Akt) pathway represents a central signalling system in the regulation of these processes. We hypothesiced that caveolin 1 is involved in the sensing of mechanic stimuly and subsequent activation of the PI3K/Akt pathway. Methods and results: Quiescent, mitogen-free rat VSMC were subjected to cyclic-stretch for up to 24 h (0,5 Hz at 120% resting length).Lysates were used for immunoblot of activated (phospho-) Akt. Akt was phosphorylated and activated after 10 min of stretch and after 24h we observed an increase in cellular proliferation as measured by propidium iodid staining and FACS analysis (16±2,1 vs. 24±2,6% of cells in S/G2 phase n=6, $p<0,05$). Transfection of cells using caveolin 1 antisense (cav1-AS) but not control AS prevented phosphorylation of Akt. cav1-AS as well as inhibitors of the PI3K (Wortmannin and LY294002) inhibited stretch-induced proliferation of VSMC (cav1-AS:18±3,1% vs. 24±2,6% cells in S/G2 phase, n=6, $p<0.05$). Transfection of cav1-AS also resulted in an increase of apoptotic cells after 24h of stretch (26±5% vs. 8±2% in control cells) as measured by dUTP-biotin nick end labeling (TUNEL).

Conclusion: Caveolin1 is essential for the stretch-induced activation of the PI3K/Akt pathway, thereby controling proliferation and apoptosis of VSMC. Caveolin 1 is an important regulator in mechanical stress induced remodeling of the vascular wall.

LIPIDS AND ATHEROSCLEROSIS

P412 Changes in serum lipids, lipoproteins and apolipoproteins in patients with acute infection

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Background: Transitory changes in the serum levels of lipids, and particularly hypocholesterolemia, have been observed in the course of acute infections. However, there are limited data on the effect of acute inflammatory response on the serum levels of apolipoproteins (Apo) AI, B, E and lipoprotein (a) [Lp(a)].
Aim: To examine the incidence of hypocholesterolemia and the changes of serum lipid parameters during acute infection in patients hospitalized in an internal medicine clinic.
Patients and methods: Serum lipid parameters were measured in 3.000 patients who were admitted to our clinic during a period of one year. Hypocholesterolemia was defined as serum total cholesterol <120 mg/dl. Hypocholesterolemic patients with acute infection were compared with 116 age and sex matched healthy individuals. Serum lipid parameters of 20 hypocholesterolemic patients with acute infection were followed up after their discharge. All values are expressed in mg/dl.
Results: Hypocholesterolemia was found in 120 patients (4%). 58 patients (48.3%) had acute infection [45 patients (77.5%) had bacterial infections, 8 patients (13.8%) viral infections and 5 patients (8.7%) kala-azar]. Compared with control patients, hypocholesterolemic patients with acute infection had significantly lower levels of total cholesterol (98±19 vs 204±42, $p<0.001$), HDL cholesterol (20±8 vs 42±8, $p<0.01$), LDL cholesterol (59±19 vs 120±36, $p<0.001$), ApoAI (64±22 vs 146±24, $p<0.01$) and ApoB (66±20 vs 102±26, $p<0.01$), whereas serum triglycerides were unaffected (127±61 vs 120±98, p=NS). Interestingly, ApoE levels were significantly higher (47±23 vs 39±11, $p<0.05$) and Lp(a) levels were significantly lower [median 3.85 (range 0.8-33.2) vs 7.9 (0.8-56), $p<0.01$] compared with the control population. During the follow-up the levels of total cholesterol, HDL cholesterol, LDL cholesterol and ApoAI were increased by 48.7% ($p<0.001$), 45.5% ($p<0.05$), 79.4% (p=0.002) and 88.3% ($p<0.001$), respectively. Furthermore, ApoE levels were significantly reduced by 36% ($p<0.05$), while Lp(a) levels were significantly increased (from a median value of 2.5 to a median value of 9.6, $p<0.05$).
Conclusion: Infection-induced hypocholesterolemia is a frequent metabolic disorder in hospitalized patients. Our data point out that Lp(a) may be a negative acute phase reactant. Furthermore, we show for the first time that serum ApoE levels are elevated during the acute inflammatory response.

P413 Linolic acid induced vascular cell adhesion molecule-1 expression depends on nuclear factor kappa-B activation

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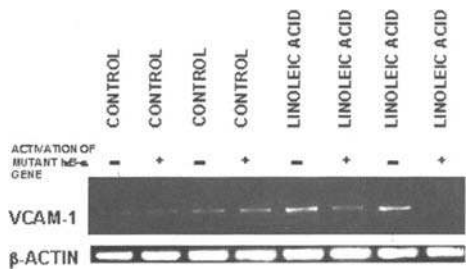
Endothelial activation is an important step in atherogenesis. In addition to established cardiovascular risk factors such as hypercholesterolemia, hypertension, diabetes mellitus and homocysteinemia, high plasma levels of triglyceride-rich lipoproteins may be an important cause of endothelial activation as well. Free fatty acids hydrolysed from core triglycerides of these particles can exert both pro- and antiinflammatory effects on the vascular wall. Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to inhibit cytokine-induced endothelial activation. In contrast, we and others have previously shown that the omega-6 fatty acid linoleate activates transcription factor nuclear factor kappa B (NF-kappa B) in endothelial cells.
In this study we show that linoleic acid stimulates vascular adhesion molecule-1 (VCAM-1) protein and mRNA expression in cultured human endothelial cells, as assessed by immunoflourescence and northern blotting. By use of cultured rat aortic endothelial cells transfected with an IkappaB super-repressor (delta N2 cells), we provide evidence that NF-kappa B signalling is required in the linoleic acid-induced VCAM-1 expression in endothelial cells, whereas other transcription factors appear to be involved in the increased endothelial plasminogen activator inhibitor-1 (PAI-1) production in response to linoleic acid.
In conclusion, these findings support the notion that linoleic acid influences the expression of inflammatory genes in endothelial cells by interference with the redox-sensitive transcription factor NF-kappa B.



P414 AT1 receptor antagonism improves hypercholesterolemia-associated endothelial dysfunction

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Hypercholesterolemia-induced AT1 receptor overexpression is thought to be a key event in the development of endothelial dysfunction. To verify this pathophysiological concept, the effect of a 6 week-treatment with the AT1 receptor antagonist candesartan (16 mg/d) on endothelium-dependent vasodilatation and serum inflammation markers was compared to the treatment with placebo or the calcium channel antagonist felodipine (5 mg/d) in 47 hypercholesterolemic patients (LDL cholesterol>160 mg/dl).
Methods and Results: Endothelial function was assessed by measurement of forearm blood flow (FBF) by venous occlusion plethysmography. FBF during reactive hyperemia was significantly improved by candesartan, whereas felodipine and placebo exerted no effect. Nitroglycerin-induced vasorelaxation and basal FBF were not altered. Blood pressure as well as cholesterol levels were not affected significantly by any drug. Serum concentrations of 8-isoprostanes, monocyte chemoattractant protein-1 (MCP-1), and soluble intercellular adhesion molecule-1 (sICAM-1) were significantly reduced by AT1 receptor antagonist treatment but not by placebo or felodipine. Levels of high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-alpha) were not altered significantly by any treatment.
Conclusions: AT1 receptor antagonism improves vascular function during hypercholesterolemia applying to endothelium-dependent vasodilatation, oxidative stress, and events involved in monocyte attraction and adhesion. Thus, AT1 receptor blockade may potentially represent a novel approach for the prevention of vascular dysfunction associated with hypercholesterolemia independent of lipid and blood pressure-lowering interventions.

P415 Effects of atorvastatin on in-stent-stenosis in normo- and hypercholesterolemic rabbits

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Background: Statins can inhibit proliferation irrespective of total plasma cholesterol levels. In-stent-stenosis goes along with an elevated and prolonged proliferation, but also inflammatory reactions with macrophages, foam cells and lymphocytes around the stent struts. Potentially, the antiproliferative and lipid-lowering effects of statins can synergistically limit neointima formation after stenting. This hypothesis was tested in normo- and hypercholesterolemic rabbits. Methods: Stents were placed in the iliac arteries of 40 rabbits according to the Schwartz-injury-model. Twenty animals were fed an 0.5% hypercholesterolemic diet, the other half was normocholesterolemic. Both groups received either atorvastatin (3 mg/kg b.w. per day) or placebo (4 groups, n=10 each). After 28 days, the animals were killed and stented segments were excised. Immunohistochemistry (bromodeoxyuridine, alpha-actin, RAM11-macrophages and von Willebrand factor) was performed, morphometric analysis was done in cuts with the stent left in place. Data were related to injury- and inflammation scores and the total drug uptake. Results: Proliferation was significantly increased in both hypercholesterolemic groups. No significant difference in proliferation was found in atorvastatin-treated animals, both normo- or hypercholesterolemic, versus controls. Apparently significant differences in morphometric results between the 4 groups disappeared when carefully relating the results to the extent of injury and the total drug uptake. Conclusion: In this animal model, atorvastatin was not able to limit in-stent-stenosis, neither via its lipid-lowering properties nor via an independent antiproliferative effect.

P416 Prevalence, distribution and correlates of thoracic aortic atherosclerosis in patients with heterozygous familial hypercholesterolemia

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Atherosclerosis of the thoracic aorta (ATA) correlates with atherosclerotic affliction of other vascular sites and prognosticates cardiovascular morbidity. In this study, multiplane transesophageal echocardiography (TEE) was employed to asssess the characteristics of ATA among an unselected population of patients (pts) with heterozygous familial hypercholesterolemia (hFH) attending the outpatient dyslipidemia unit of our department.

Methods: Between Jan 1999-Jan 2002 TEE was performed in 82 pts with hFH (aged 41±11 years, 41 men). The studies of the thoracic aorta were stored on tape and were reviewed off-line in a blinded fashion. ATA was graded by a modified Ribakove score as: grade 1: normal intima; 2: increased intimal echodensity without thickening or irregularity; 3: single atheroma of ≤3 mm maximum width; 4: >1 atheromas ≤3 mm; 5: ≥1 atheromas >3 mm; 6: mobile/ulcerated plaques. ATA was scored separately in each aortic segment (ascending, arch, descending) and each pt was assigned a single score based on the largest identified lesion overall. Grades >3 were regarded as representing significant ATA.

Results: Twenty-one pts had never received hypolipidemic treatment prior to the examination; 14 pts had a history of clinically manifest coronary artery disease. Mean serum LDL-cholesterol was 265±91 mg/dl. ATA grade was 1 in 1 pt, 2 in 31, 3 in 20, 4 in 17, 5 in 12 and 6 in one pt. The descending thoracic aorta was the commonest single location of the major grade-defining ATA lesions (n=25, 30.5%), followed by the aortic arch (n=13) and the ascending thoracic aorta (n=4); among the remaining cases, lesions of equal severity were hosted by 2 aortic segments in 21 and by all 3 segments in 19 pts. Ordinal regression analysis performed on demographic, clinical and biochemical variables identified age (p=0.02), postmenopausal status (p=0.008), lack of previous therapy (p=0.04), and serum LDL-C level (p=0.04) as independent positive correlates of ATA severity; Intriguingly enough, a history of cholecystectomy due to gallstone disease (p=0.02) was a significant negative correlate of ATA severity.

Conclusions: ATA is highly prevalent in unselected pts with hFH. The duration of the disease and the success of lipid-lowering treatment influence ATA severity in this patient population. In view of potential therapeutic implications entailed by significant ATA, the traits indicating a high likelihood of its presence might be exploited in order to select hFH patients for evaluation of the thoracic aorta by TEE.

P417 Role of oxysterol stereospecificity in patients with coronary artery disease

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Circulating oxidized LDL is a known marker for identifying patients (pts) with coronary artery disease (CAD). While unmodified cholesterol does not exert toxicity, oxysterols as one compound in oxLDL are believed to be mainly responsible for endothelial toxicity. We developed a method to quantify circulating oxysterols in human plasma by gas chromatography. Validation for the identity of chromatography peaks was achieved by mass spectometry.

In this preliminary study we included pts who underwent coronary angiography to either exclude (Control) or secure the diagnosis of CAD. Pts with coexisting diseases other than diabetes or hypertension were excluded from this study. Total LDL cholesterol was higher in the Control group (130.4 vs. 129.5 mg/dl). The table shows, that the only significant difference between the 2 groups is represented by the 5-beta-epoxide plasma levels ($p<0.05$) and a trend in 7-beta-OH-cholesterol (p=0.11). Both were elevated in pts with CAD. In parallel we performed in-vitro studies using human arterial endothelial cells (HAECs). We found induction of apoptosis through caspase-3 like enzymes by oxysterols. This effect was highly dependent on the stereospecificity of oxysterols: beta-isomers of epoxide or 7-OH-cholesterol induced up to 3-fold higher amounts of apoptosis and mitochondrial cytochrome C release in HAECs compared to their alpha-isomers.

Free Plasma-Oxysterols [ng/ml]

mean (± SEM)	Control (n=4)	CAD (n=9)
7-alpha-OH-cholesterol	66.8 (9.9)	64.7 (21.3) NS
7-beta-OH-cholesterol	5.9 (5.7)	19.5 (17.0) NS
5-alpha-epoxide	67.6 (12.1)	74.2 (27.0) NS
5-beta-epoxide	4.6 (2.5)	58.3 (21.8) *
25-OH-Cholesterol	2.5 (1.5)	3.4 (1.1) NS

NS not significant, *$p<0.05$

Conclusion: Beta-isomers of oxysterols were significantly elevated in plasma from pts with CAD. In-vitro studies demonstrated the importance of oxysterol stereospecificity concerning their potential to harm endothelial cells. While analysis of oxysterol levels in a large cohort of CAD pts has to further solidify their role in atherosclerosis, stereospecific effects might be of superior importance in the mechanism of atherogenesis.

P418 Effects of atorvastatin treatment on vascular endothelium, inflammatory process and heart function, in patients with heart failure

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Background: Heart failure is characterized by endothelial dysfunction and increased serum levels of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor (TNF-a) and soluble vascular cell adhesion molecule (sVCAM-1). Statin treatment, seems to restore endothelial function in hypercholesterolemic patients while its anti-inflammatory effects are unknow. Purpose of this study was to investigate the effect of atorvastatin treatment on endothelial function and inflammatory processin patients with heart failure.

Methods: In this double blind placebo controlled study, 38 patients with heart failure (30 males 8 females, aged 65±2 years old) were enrolled. 20 patients received atorvastatin 10mg/day (group A) while 18 patients received placebo (group B) for 4 weeks. All patients were NYHA II to IV. Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to maximal flow during reactive hyperemia. Endothelium independent flow (NTG%) was expressed as the % change from baseline to post sublingual nitroglycerin administration flow. Serum levels of IL-6, TNF-a and sVCAM-1 were determined with ELISA. All values are expressed as mean±SEM

Results: FMD was significantly improved in group A (from 44.1±5.4 to 96.1±13.1% $p<0.01$) while remained unaffected in group B (from 51.9±5.6 to 47.9±6.35%). Serum levels of IL-6, TNF-a and sVCAM-1 were decreased in group A (from 7.05±0.7, 3.4±0.3 and 585.5±50.1 to 5.9±0.51 pg/ml $p<0.05$, 2.7±0.2 pg/ml $p<0.05$ and 490.4±51.0 ng/ml p=NS) while remained unaffected in group B (from 7.52±0.81, 4.35±0.76 and 698.46±69.1 to 6.5±0.88 pg/ml, 4.45±0.71pg/ml and 585.08±75.3ng/ml p=NS for all, respectively).

Conclusions: Treatment with atorvastatin improves endothelia function in patients with heart failure. Atorvastatin treatment also decreases serum levels of IL-6 and TNF-a in those patients. These findings indicate that statins might be useful in patients with heart failure by affecting endothelial function and inflammatory process.

ANGIOGENESIS

P419 Human tissue kallikrein: a new bullet for therapeutic angiogenesis

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Therapeutic angiogenesis represents a new promising strategy for the treatment of ischemic disease. Following successful application in animal models, the strategy has been transferred from the bench to the bedside. However, clinical results did not result in the level of efficacy for which researchers had hoped. Mechanistic approaches based on molecules capable of completing the angiogenic program may help overcoming the present impasse. We evaluated the pharmacological profile and the vascular and molecular targets of human tissue kallikrein (hTK), a protease that cleaves the vasodilator peptides kinins from kininogen. Local adenovirus-mediated hTK gene (Ad.CMV-hTK) transfer increased capillary density in mouse normoperfused limb muscle. A infecting dose of 10^5 pfu increased muscular capillary density by 23%, while 10^4 pfu was not effective. The angiogenic response to hTK reached a plateau (53% increase in capillarity) in a range between 10^7 and 10^9 pfu. Similar effects were observed by delivering hTK in a plasmid vector (980±41 vs 580±20 cap/mm^2 in contralateral non-injected muscle, $P<0.01$). Ad.CMV-hTK also increased arteriole density from a value of 8±2 art/mm^2 in controls to 20±3 and 21±4 art/mm^2 at 2 and 8 weeks post-injection ($P<0.01$), while no significant change was detected in muscles injected with reporter gene Ad.CMV-Luc. Morphometric analysis documented that the increase encompasses arterioles up to 164 μm of internal diameter. Expression of angiogenesis-related genes was evaluated by microarray analysis in muscles injected with Ad.CMV-hTK or Ad.CMV-Luc. We found that transfection with hTK gene results in induction of VEGF, angiopoietin 2, plasminogen activator receptor 2, plasminogen activator inhibitor, and thrombospondin genes. In separate experiments, dominant negative Akt gene was coadministered with Ad.CMV-hTK to see if Akt is implicated in the angiogenic action of hTK. Dominant negative Akt blunted the microvascular effects of hTK (767±59 vs 962±16 cap/mm^2, $P<0.02$) while wild-type Akt gene did not produce significant effects (858±57 cap/mm^2). These results indicate that neovascularization promoted by hTK derives from capillary sprouting and collateral artery growth, which is consistent with induction of both angiogenesis and arteriogenesis. The abilty of hTK to interfere with various angiogenesis modulators may account for the formation of a persistent, well-tempered neovascularization. The pleiotropic kallikrein-kinin system may represent a new target for therapeutic angiogenesis.

P420 Sonic hedgehog induces angiogenesis, upregulates VEGF and angioproteins, and is postnatally activated in response to skeletal muscle ischaemia

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Sonic hedgehog (Shh) is a morphogen that regulates epithelial-mesenchymal interactions in many tissues during embryonic development. We found that systemic administration of Shh induced upregulation of the Shh receptor Ptc1 in heart and peripheral vasculature, indicating that the Shh pathway can be activated in vivo in adult animals. In vitro studies, showed no effect of Shh on endothelial cell migration or proliferation. In vivo, however, Shh was found to induce robust neovascularization in the murine corneal model of angiogenesis. Similarly, Shh was also able to induce angiogenesis, augmented blood flow recovery and limb salvage in operatively induced hindlimb ischemia in aged mice. The angiogenic response to Shh appears to occur indirectly through the activation of Ptc1 on neighboring fibroblasts. Shh stimulation of human fibroblasts in vitro increases mRNA synthesis of VEGF121, VEGF165, VEGF189, Ang-1 and Ang-2. Production of VEGF165 protein from human fibroblasts is also increased by Shh. Then, we studied whether the endogenous Shh pathway, so important during embryogenesis, plays a physiologic role in muscle regeneration following ischemia in adults. We demonstrated that, while no Shh is expressed under baseline, quiescent conditions, muscle regeneration induced in response to ischemic injury is associated with activation of the Shh signaling pathway. Shh was strongly activated in skeletal muscle after ischemia and its receptor Ptc1 was upregulated in interstitial mesenchymal cells within the ischemic area, indicating that these cells respond to Shh and that the Shh pathway is functional. The Shh responding cells produced VEGF under ischemic conditions and treatment with a Shh blocking antibody inhibited the angiogenic response and the upregulation of VEGF.

Conclusions: Our study shows for the first time that the Shh signaling may be functional in adult and fully differentiated muscular tissues and has a regulatory role on angiogenesis during muscle regeneration following ischemia. In addition, the discovery of angiogenic activity for Shh, combined with its known morphogenic functions in development, suggests that Shh may coordinate epithelial/stromal interactions with the ingrowth of vasculature during development. The ability of Shh to promote limb salvage in aged mice, through the enhancement of blood flow and capillary density, suggests that Shh may merit further investigation as proangiogenic therapy for ischemic disorders.

P421 Adventitial delivery of the gene for an amphipathic peptide using optimized gene transfer conditions

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Amphipathic peptides are animal peptide antibiotics that inhibit mitochondrial functions and thus tumor growth in animal models. Therefore they could be of use in preventing cell proliferation and restenosis. The aim of this study was to investigate the potential therapeutic effects of locally delivering the gene for an amphipathic peptide into a porcine injury model. Extensive investigations were performed to achieve maximum gene transfer efficiencies for non-viral vectors in vivo. Alos, further improvements of the needle injection catheter for local drug delivery was achieved by increasing the length, flexibility and modification for the use with guide wire.

Numerous DNA/liposome ratios for 17 different liposomes and adjuvant agents were tested in quiescent smooth muscle cells for maximum transfer efficiencies. The gene was inserted into an expression vector plasmid and mixed with DOCSPER liposomes in a ratio of DNA to liposome of 1:10 according to optimal results achieved. Domestic pigs (n=24) were fed a normal chow diet. Porcine iliac artery segments were balloon-injured on both sides in vivo in a standard manner. The needle injection catheter was used to deliver the gene locally into the adventitial of injured artery on one side in each pig; the other side served as a control and was only balloon-injured. Arterial segments were excised at 7 days, 3 weeks or 4 months. Tissues were examined at histology, with computer-assisted morphometry and PCR/RT-PCR. Similar experiments with the β-galactosidase reporter gene served to confirm expression of transfected gene. A reduction in neointimal hyperplasia in arteries treated with the gene of the amphipathic peptide could be shown. At 21 days, neointimal area in balloon-injured segments was 0.32±0.13mm^2 SEM compared with a reduced neointimal area in treated segments: 0.05±0.02mm^2 SEM ($p < 0.05$). Gene transfer efficiency was up to 15% in the adventitia using optimized transfer conditions for non-viral gene transfer.

In conclusion, the gene for an amphipathic peptide was successfully and safely delivered using the needle injection catheter resulting in reduction of neointimal formation. Gene transfer effciciencies were comparable to those achieved by viral gene transfer. Such peptides may therefore have therapeutic potential in the prevention of restenosis.

P422 Alpha 5 beta1 is a new interesting target for the treatment of SMC migration and invasion dependent vascular pathologies

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Migration and invasion of human arterial smooth muscle cells (haSMC) are essential steps during the development of atherosclerosis, restenosis after vascular intervention, and transplant vasculopathy. Due to their contact to the surrounding extracellular matrix integrins have been previously shown to regulate cell phenotype and cell function. There is evidence that differential expression of integrins has a major impact on the invasive phenotype of myocytes. For this reason, a quiescent and a migrating, invading haSMC phenotype was induced by cell culture conditions. Using a Boyden Chamber model migrating and invading haSMCs in contrast to quiescent haSMCs were capable to migrate towards chemoattractive stimuli and even capable of invading through a basement membrane equivalent. FACS analysis of integrin expression between both phenotypes showed a strong upregulation of alpha 5 beta 1 (13.1x) as well as alpha v beta 3 (3.4x) in proliferating haSMCs in comparison to quiescent haSMCs. Other integrins analysed (alpha 2, alpha 3, alpha 4, alpha IIb) did not show significant differential regulation. In further functional assays, inhibition of alpha 5 beta 1 led to inhibition of migration in cell sedimentation manifold assay (CSM, -29±8%), Boyden chamber assay (-49±16) and collagen contraction (-125%). In contrast, inhibition of alpha v beta 3 had no effect on inhibition of haSMC migration in CSM assays but reduced invasion in the Boyden chamber (-45±8%). Interestingly alpha v beta 3 caused even a significant stimulation of collagen contraction in comparison to control (+52%). We conclude that alpha 5 beta 1 is a new interesting target for the treatment of SMC migration and invasion dependent vascular pathologies.

P423 Angiogenesis in human atherosclerotic carotid plaques is associated with expression of macrophage migration inhibitory factor 1-alpha

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Background: Neovascularization within atherosclerotic plaques may play a role in the pathogenesis of plaque progression and vulnerability.The purpose of this study was to determine if the existence of intraplaque vessels may be associated with the expression of macrophage migration inhibitory factor 1-alpha(MIF), a protein known participate in inflammatory and immune responses. It also plays a key role in tumor angiogenesis.
Methods: Carotid endartherectomy and vessel samples were collected from 21 patients and 4 young accident victims controls (co) and were assessed for histological classification by Stary (SI-VI). Immunohistochemistry was performed by using a specific monoclonal antibody (mAb) to MIF and to visualize 1.intraplaque vessels, endothelial cell (EC) specific mAb to CD34 and vWf, 2.Monocytes/macrophages (Mo), mAb to CD68 and 3.vascular smooth muscle cells (VSMC), mAb to alpha-actin were used. The extent of neovascularization was graded on scales of d0 to d3 in terms of specific staining intensity und distributions in the wall.
Results: All specimens from patients contained advanced plaques (S IV - VI) with neovessels of degree d3 in the shoulder and/or cap regions of 13 plaques (52%), d2 in 6 plaques (24%), d1 in 2 plaques (8%) and no vessels in intima or media from the 4 samples of the co (16%).Strong MIF staining was localized only in areas of marked neovascularization and inflammation (d3,d2) and was expressed exclusively by CD68-positive Mo and CD34/vWf-intraplaque EC. There was no detection of MIF expression in alpha-actin-positive VSMC. In plaques with small or no expression of neovessels (d1,d0) only a weak or no MIF staining respectively was observed.
Conclusion: The results demonstrate a marked upregulation of migration inhibitory factor 1-alpha in close correlation to Mo infiltration and neovesssels in plaques suggesting a pivotal role of MIF in neoangiogenesis and plaque inflammation.

P424 Platelet-activating factor is detectable in human carotid atherosclerotic plaques and correlates with intra-plaque neoangiogenesis

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Plaque instability is considered the major factor in the development of thromboembolic sequelae in atherosclerotic lesions. Several factors have been implicated in plaque instability, including the infiltration of inflammatory cells and the process of neoangiogenesis. Platelet-activating factor (PAF), a phospholipid mediator of inflammation, has been recently shown to mediate endothelial cell recruitment triggered by TNF-a and VEGF and to contribute to neoangiogenesis. In the present study we evaluated the presence of PAF and its potential role in neovascularization within atherosclerotic plaques. Endarterectomy specimens of carotid plaques were obtained from 18 patients with previous signs or symptoms of cerebrovascualr disease; 6 specimens of carotid artery and 12 of aorta from kidney donors were used as controls. Adjacent cross-sections were processed for PAF extraction and histological analysis.
Advanced atherosclerotic lesions were always present in endarterectomy specimens. The amount of PAF extracted from the carotid plaques (266.65 + 40.07 pg/100 mg dry tissue; mean + SE) was significantly higher than that extracted from controls (4.72 ± 2.31 pg/100 mg dry tissue; mean ± SE). The mass spectrometric analysis of PAF-bioactive lipid extracts from carotid atheromas, but not from normal arteries, showed the presence of several molecular species of PAF, including alkyl-PAF C16 and alkyl-PAF C18, which are angiogenic in vivo. The levels of PAF significantly correlated with the infiltration of CD68-positive macrophages and with the extent of neovascularization, detected as Factor VIII-related antigen immunoreactive cells, analysed by morphometry. The amount of PAF also correlated with the area positive for avb3integrin (considered an endothelial cell proliferation marker) and with the extension of TNF-a immunoreactivity. The lipid extracts of atherosclerotic plaques containing high levels of PAF-bioactivity, but not those of control arteries, were angiogenic in a murine Matrigel model. WEB 2170, a PAF receptor antagonist, significantly prevented angiogenesis induced in mice by the lipid extracts of atherosclerotic plaques. In conclusion, the present results demonstrate that PAF is detectable in carotid plaques, that PAF amount correlates with intraplaque angiogenesis and inflammation and that PAF extracted from atherosclerotic plaques induces angiogenesis in mice, suggesting that an enhanced concentration of PAF may contribute to intra-plaque neoangiogenesis.

P425 Protease activated receptor-2 (PAR-2) mediates angiogenesis and ameliorates post-ischaemic recovery of mouse hindlimbs

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Background: Protease Activated Receptors (PARs) form a novel class of G-protein-coupled receptors that are activated by proteolytic cleavage able to unmask an N-terminal sequence acting as a tethered ligand. Synthetic peptides may activate PARs in the absence of proteolysis. PAR-2 is highly expressed by the cardiovascular system and mediates endothelial cell proliferation, vasodilation, and plasma extravasation, three mechanisms able to favour neoangiogenesis. **Aim:** To investigate the angiogenic potential of PAR-2 in hindlimb skeletal muscles.
Methods: Unilateral limb ischemia was induced in anaesthetized CD-1 mice by removing the left femoral artery. Modulation of PAR-2 gene expression by ischemia was evaluated by RT-PCR. Then, the PAR-2 activating peptide (AP, n=8) SLIGRL-NH2 or control reverse peptide (RP, n=7) was daily injected (300 nmol/20 μL) into the left adductor for 21 days from surgery. Additional groups of mice received trypsin (1.5 nmol, n=9), a protease able to preferentially activate PAR-2, or vehicle (n=7). Tail-cuff SBP and HR were measured in conscious mice basally and weekly after surgery. Hindlimb blood flow (BF) of anaesthetized mice was evaluated by colour laser doppler (Lisca, Sweden) every 7 days from ischemia induction. Anaesthetized mice were perfusion-fixed at 21 days and both adductors harvested for histologic analysis of capillary density.
Results: One day of ischemia doubled mRNA level. Up-regulation was maintained for 7 days. Systemic hemodynamic was not affected by ischemia or pharmacological treatments. AP ameliorated limb BF recovery (63±12 vs. 32±15% in RP, $P<0.05$) and trypsin had a similar effect (62±11% vs. 33±10% in saline, $P<0.05$). Both AP and trypsin increased capillary density in the ischemic injected muscle (AP: 1213±97 vs. 868±82 cap/mm^2 in RP, $P<0.05$; trypsin: 1107±62 vs. 715±79 cap/mm^2 in saline, $P<0.01$), without affecting capillarity of contra-laterals (data not shown).
Conclusions: Our study is the first one to demonstrate the angiogenic potential of PAR-2. In perspective, potentiation of PAR-2 signaling might be exploited for the treatment of ischemic disease.

TISSUE DOPPLER IMAGING

P426 Longitudinal ventricular function: normal values of annular and myocardial velocities measured with colour tissue Doppler imaging

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Impaired longitudinal function may be a marker of early myocardial disease. Colour tissue Doppler imaging (TDI) is a new method of assessing left ventricular (LV) and right ventricular (RV) long axis function. Age- and sex-related reference values for atrioventricular annular and regional myocardial velocities are essential for the clinical use of the method.
Methods: 123 healthy subjects (age 57±19 years, range 22 to 89 years, 59 women) underwent echocardiography including colour TDI using GE Vingmed System Five and Vivid Five scanners with post-processing analysis (Echopac 6.3). For the assessment of LV longitudinal function, regional myocardial velocities were measured in basal and mid-wall segments of lateral, septal, anterior, inferior, posterior and antero-septal LV walls. Mitral annular velocities were measured from six positions at corresponding sites of the mitral annulus. For the assessment of RV longitudinal function, myocardial velocities were measured in basal and mid-wall segments of free RV wall, and tricuspid annular velocities were calculated at the lateral site of the tricuspid annulus. At each position, systolic (Sm), early diastolic (Em) and late diastolic (Am) velocities were measured, and the Em/Am ratio was calculated.
Results: Subjects were classified into 4 groups aged 20-39, 40-59, 60-79, and 80-89 years. Mitral annular and regional LV myocardial Sm and Em velocities progressively decreased with age ($p<0.001$), and Am velocities, while very low in the youngest age group, significantly rose in patients over 40 years of age ($p<0.001$). The Em/Am ratio declined with ageing ($p<0.001$). Mitral annular Em velocity and the Em/Am ratio strongly correlated with age ($r=-0.79$ and $r=-0.77$, $p<0.001$). There were no differences between age groups in Sm velocities measured at the tricuspid annulus and free RV wall (p=NS) but the pattern of age-related changes of diastolic velocities and Em/Am ratios was the same as in the left ventricle. Women in the two middle age groups had lower TDI velocities than men ($p<0.05$).
Conclusions: This study establishes age- and sex-related reference values of atrioventricular annular and myocardial velocities measured with colour TDI. Systolic longitudinal LV function declines with age, whereas RV function remains unaffected. A reversal in the pattern of diastolic atrioventricular annular and myocardial velocities suggests that LV and RV diastolic function deteriorates with age.

P427 Opposite effects of coronary artery disease and hypertrophic cardiomyopathy on left ventricular long axis physiology during dobutamine stress

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Background Early diastolic long axis lengthening velocities are depressed in hypertrophic cardiomyopathy (HCM). From a clinical standpoint, these have been proposed as a means of selecting phenotypically normal relatives of HCM patients for counselling. Pathophysiologically, the reason for this abnormality in HCM is not known, although proposed mechanisms include subendocardial ischaemia, myocardial fibrosis or disarray.
Methods We digitised M-Mode measurements of the septal long axis in 23 patients with HCM, 17 normal subjects and 22 patients with coronary artery disease (CAD) of the left anterior descending artery at rest and at peak stress.
Results The lengthening velocity was reduced not only in HCM (3.5 ± 1.9 cm/s) but also in CAD (4.1 ± 2.5 cm/s, $p<0.001$ and $p<0.01$ respectively). Long axis amplitude was also depressed in both groups. With dobutamine stress, the lengthening velocity increased by 3.5 ± 1.8 cm/s ($p<0.001$) in normals, by 2.8 ± 2.5 cm/s ($p<0.001$) of rest in HCM but not in patients with CAD (0.5 ± 2.1, p=NS). Increment in long axis total amplitude was subnormal in CAD and HCM. However, the increment in lengthening velocity was higher with stress for a corresponding change in amplitude in HCM (60% lying above the 95% confidence interval of CAD). Post-ejection shortening developed or worsened in all CAD patients but not in any with HCM.
Conclusion Depression of peak early lengthening velocity is not specific for HCM but occurs equally in CAD. This is not due to subendocardial ischaemia in HCM, because unlike CAD, its velocity increases with stress and there is no aggravation of post-ejection shortening with stress. The HCM heart shows evidence of greater elastic recoil per unit deformation than heart of patients with CAD, compatible with increased muscle stiffness due to fibrosis or disarray.

P428 Additional estimation using pulsed Doppler myocardial imaging improves the reproducibility of measurement of myocardial velocity gradients

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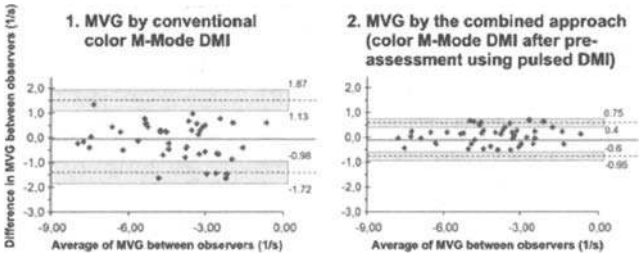
Background: Peak negative myocardial velocity gradient (MVG) across the left ventricular wall is an important indicator of regional diastolic performance. The reproducibility of MVG assessment by color M-Mode Doppler myocardial imaging (DMI) is still unsatisfactory, restraining its use in clinical practice.
Aim of this study was to improve the interobserver variability of MVG measurements.
Methods: Two-dimensional color-coded DMI cineloops were acquired in 50 consecutive patients in parasternal long axis view (Sonotron GE, Echopac 6.3.2). The maximal early diastolic MVG of the posterior basal wall was determined successively by 2 independent investigators in 2 ways: using directly standard anatomic color M-Mode DMI (mean off-line analysis time of 2 minutes) and by the same technique, but guided by a preliminary MVG estimation with pulsed DMI using 4 measurement sets within ventricular wall (mean analysis time of 4.5 minutes).
Results: Additional use of pulsed DMI provided a higher linear correlation between pairs of measurements (r = 0.98, SEE = 0.34 1/s) compared to MVG determination by conventional color M-Mode DMI (r = 0.92, SEE = 0.69 1/s). Accordingly, as displayed in the picture, the agreement limits by the method of Bland and Altman of the combined method [-0.78 1/s (95% CI of -0.95 1/s to -0.6 1/s) to 0.57 1/s (95% CI of 0.4 1/s to 0.75 1/s)] were clearly superior to those shown by color M-Mode DMI without B-Mode pre-assessment [-1.35 1/s (95% CI of -1.72 1/s to -0.98 1/s) to 1.5 1/s (95% CI of 1.13 1/s to 1.87 1/s)].



Interobserver agreement for MVG.

Conclusions: These study results recommend the utility of an initial estimation by pulsed DMI to achieve a clinically acceptable reproducibility of MVG measurements.

P429 Influence of myocardial SPET viability on evaluation of regional systolic performance with color tissue Doppler imaging

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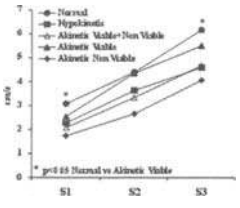
Aim of the study was to evaluate the influence of SPET myocardial viability on Color Tissue Doppler Imaging (C-TDI) measurements of regional systolic function in patientes with severe left ventricular dysfunction.
Methods: Twelve patients (mean age 65±5 years; 9 men) with post-ischemic dysfunction (mean ejection fraction 28±4%) underwent, in the same week, 99mTc tetrofosmin SPET (rest-NTG) and dobutamine C-TDI. Regional wall motion was graded [1=normokinetic (N), 2=hypokinetic (H), 3=akinetic (A)] using a 18 segments/patient model, and peak systolic velocities (S) was measured off-line with C-TDI at rest (S1), low dose (S2) and high dose (S3) of dobutamine infusion. Regional myocardial viability was defined by the presence of >70% of 99mTc tetrofosmin uptake at rest or by >10% improvement after NTG.
Results: In the 216 segments analysed feasibility of C-TDI was 97% at rest and during dobutamine infusion. In every step of dobutamine infusion the values of S were significantly higher ($p<0.05$) in N than in H and A segments (Figure 1), while no difference were observed between H and total A segments (p=n.s.). In A segments with evidence of viability higher value of S1 (2.56±1.32 vs. 1.75±1.26, p=0.015), S2 (4.36±2.09 vs. 2.65±1.75, p=0.002) and S3 (5.52±2.80 vs. 4.06±2.45, p=0.048) were observed with respect to non viable A. There were no differences in S2 between N and A viable segments (p=n.s.).



Conclusions: Dobutamine C-TDI is a feasible modality to study regional inotropic reserve in patients with severe ventricular dysfunction. Myocardial SPET viability influences S values in severely dysfunctional segments, but not in H regions.

P430 Relation between surface electrocardiogram and site of earliest/latest motion in DCM and ICM patients with LBBB – a Doppler myocardial imaging study

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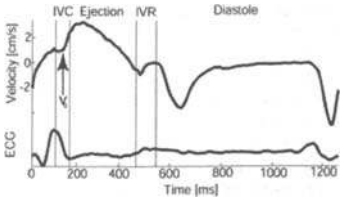
Doppler Myocardial Imaging(DMI) has been proposed to guide cardiac resynchronisation therapy(CRT). It might provide new insights in the relation between electrical and mechanical left ventricular (LV) activation and help to identify the optimal pacing site.
Aim: To identify the onset of systolic motion throughout the myocardial walls with DMI in ischemic (ICM)/idiopathic dilated cardiomyopathies(DCM) with LBBB and normals (nls) and compare this with QRS width/axis.
Methods: Colour DMI data(>150 frames/s)from 10 pts with DCM/LBBB(age 52±14y,EF 22±8%),10 pts with ICM/LBBB(age 64±11y,EF 30±8)and 10 nls(age 51±15y,EF 69±11%) was post processed to determine the time from onset of QRS to the onset of regional systolic velocity(Vo). Analysis was performed on custom made software enabling exact and reproducible timing of global cardiac events. Mechanical activation of sept, lat, inf, ant, post walls of the LV was compared with QRS width and presence of left axis deviation.
Results: No significant correlation was found between QRS width/axis and site of earliest/latest Vo. QRS width was 79±12ms (nls),169±29ms (DCM),155±26ms (ICM)with 0%,60% and 80% pts with left axis deviation respectively.Both regions of earliest/latest Vo were variable. Dominant region for earliest Vo was apical-mid sept(in 60% of nls(94±13ms), in 50% of DCM(147±41ms)and in 60% of ICM(126±18ms))while 100% of nls (148±25ms), 80% of DCM (226±48ms) and 70% of ICM (171±43ms) had latest Vo in the basal post wall.



ICM: Basal segment inf wall velocity.

Conclusions: Region of latest Vo in nls was always posterior wall. However latest Vo in DCM and ICM with LBBB and earliest Vo in all groups was heterogenously spread. Since there was no correlation with QRS with/axis, selecting pts for CRT solely on QRS with/axis might have its limitations.

P431 Myocardial strain after cumulative Ischaemia: tissue Doppler evidence of preconditioning?

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Experimentally, ischaemic myocardium has altered systolic and diastolic function, though walk-through angina or preconditioning is well recognised, and difficult to identify by echocardiography (echo). The timing of repeated ischaemic episodes is also unclear. We investigated which tissue Doppler parameters could identify this phenomenon.

Methods: 14 patients (I)(13 men) age 57±9 yrs with IHD (>75% area stenosis in >2 major vessels, and no history of MI), and 12 controls(C) (10 men) age 56±8 yrs with normal angiography, underwent 2 maximal symptom-limited exercise (ex) tests(Ex1 and 2) 1 hour apart (Bruce protocol). All had transthoracic echo (Vingmed System V) at baseline, immediately post ex, and at intervals up to 1 hour after each test. Digital loops were analysed off-line for tissue Doppler velocity and strain-rate parameters.

Results: Chest pain and ischaemia limited both tests for I. Ex2 was longer for I (447±115 v 385±122s; $p<0.01$). C ex time and workload was similar in both tests, but C Ex1 longer than I Ex1 (475±143 v 385±122s; $p<0.05$) and had higher workload (30.2±2.0 v 28.5±4.2 x10^3 mmHg/min; $p<0.01$). For Ex2, I had similar ischaemia and workload (ns) but exercised for longer (447±114 v 385±121s; $p<0.01$). The absolute changes in peak (pk) systolic velocity (V) from baseline to pk ex were different between groups for Ex1 (C>I) (3.2±2.0 v 1.0±3.0 cm/s; $p<0.05$) but were unchanged for Ex2 (2.0±2.0 v 1.9±3.0 cm/s; ns). Early and late diastolic strain (S) parameters showed differences between C and I after Ex1 (Table; basal anterior segment) which persisted for 60 mins. Following Ex2, this lasted only 15 mins.

Diastolic Strain after exercise

	Ex1 pk	Ex1 15m	Ex1 30m	Ex1 60m	Ex2 pk	Ex2 15m	Ex2 30m	Ex2 60m
dE S I	-6.0±7.0*	-3.1±5.0*	-3.0±5.0*	-4.1±7.0*	-1.3±5.0	-3.2±5.0*	-2.5±9.0	-2.5±5.0
dE S C	1.0±5.0	2.0±7.0	0.6±4.0	2.7±5.0	1.4±7.0	2.3±5.0	-1.6±6.0	-3.1±6.0
dA S I	-1.8±4.0*	-1.5±2.0*	0.5±4.0	-0.5±3.0*	-2.8±5.0*	-2.0±4.0*	0.3±3.0	-0.3±6.0
dA S C	2.0±5.0	2.3±4.0	1.4±3.0	1.9±5.0	0.8±5.0	2.2±4.0	1.1±5.0	-0.6±6.0

*$p<0.05$; Ischaemia (I) vs Control (C); dE S changes in early diastolic strain; dA S changes in late diastolic strain

Conclusion: This biphasic response in S, E and A associated with increased ex time, cardiac workload and improved regional V after Ex2 may describe tissue Doppler evidence of myocardial preconditioning at a time previously associated with myocardial stunning.

P432 Wall motion abnormalities in ischaemic and scarred myocardium. Do strain and strain rate patterns differ?

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Background: In the clinical setting, the site and size of an acute myocardial infarct (MI) is often determined by visually assessing wall motion abnormalities in the echocardiographic image. However, this may be misleading if regional dysfunction is (in part) due to previous events. I this study we therefore investigated typical myocardial deformation patterns of acute and old MI by Strain Rate Imaging, a new tissue Doppler based method to non-invasively measure regional function.

Methods: Two patient groups were investigated: a) 30 acutely ischaemic infarct patients (iPAT) on admission to the emergency room, b) 37 patients with infarct scars (sPAT) of at least 25 volume% per segment (SEG). In iPAT, ischaemic SEG were determined by a blinded read of the coronary angiogram. In sPAT, scar was defined by late enhancement in magnetic resonance imaging. In all PAT, colour tissue Doppler loops were acquired from an apical four, three and two chamber view and stored digitally. Off-line evaluation included calculation of strain (S) and strain rate (SR) curves for the basal, medial and apical SEG of all six left ventricular walls. S and SR parameters in both systole and diastole as well as the visual impression of the curves were compared between iPAT and sPAT and to data of 20 healthy volunteers.

Results: Distribution of MI site and size was comparable in the two PAT groups. Compared to normals, systolic S was sign. reduced in both iPAT and sPAT (-16.6s-1 vs. -5.6 s-1 and -2.8 s-1, resp., $p<0.01$). Systolic stretching occurred in SEG of both iPAT and sPAT (23% vs. 27%, resp., n.s.). Post systolic shortening occurred in approximately one fourth of SEG in normals but was only 7% of systolic S. In iPAT and sPAT, it reached 40% and 86%, respectively ($p<0.01$). In the visual assessment, systolic and diastolic changes did not differ significantly between diseased SEG in iPAT and sPAT. Normal SEG in PAT showed the same S and SR patterns as SEG in healthy volunteers.

Conclusion: Our data suggest, that SRI sensitively shows significant changes in myocardial deformation patterns during acute ischaemia and after MI. Those changes, however, appear to be uniform and dependent on the amount of myocardial damage rather than being specific for the particular condition.

P433 Differentiating ischaemic and idiopathic dilated cardiomyopathy using left ventricular long axis function during dobutamine stress

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Background: Subendocardial longitudinal fibres are sensitive to ischaemia. Interference with the timing of long axis motion during ischaemia causes incoordinate left ventricular (LV) contraction.

Aim: To study long axis response to dobutamine stress in patients with ischaemic- (Is-DCM) and idiopathic dilated cardiomyopathy (Id-DCM).

Methods: 18 patients with Id-DCM (EDD 6.6±0.7cm, ESD 5.5±0.7cm, aged 63±12 years) were compared with 25 patients with Is-DCM (EDD 7.0±0.8cm, ESD 5.9±0.9cm, aged 63±9 years), and 17 controls (EDD 5.0±0.4cm, ESD 3.3±0.6cm, aged 58±11 years). Transthoracic septal long axis M-mode echograms with an ECG (lead II) were obtained at rest and peak dobutamine stress. The time from the q wave of the ECG to the onset of shortening (q-OS), total long axis amplitude, shortening and lengthening velocities, and post-ejection shortening (PES) were measured.

Results: Rest. In controls, q-OS was 81±11ms, total amplitude 1.4±0.3cm, shortening velocity 6.9±1.6m/s, lengthening velocity 5.7±1.4m/s, and PES was absent. In Id-DCM, q-OS was longer than controls (139±46ms, $p<0.001$), total amplitude and shortening velocity were reduced (0.9±0.3cm and 3.3±1.0m/s, both $p<0.001$), lengthening velocity was not different (4.9±1.9m/s), and PES was increased (0.9±1.2mm, $p<0.01$). In Is-DCM, q-OS was not different from Id-DCM (127±34ms), total amplitude and shortening velocity were lower (0.7±0.3cm, $p<0.05$ and 2.1±1.2m/s, $p<0.01$), lengthening velocity was reduced (1.5±1.8m/s, $p<0.001$), and PES was not different (0.8±0.1mm).

Response to stress

Variable	Controls	Id-DCM	Is-DCM
q-OS (ms)	- 46 ± 13	- 52 ± 33	+ 17 ± 25 ** °°
total amplitude (cm)	+ 0.3 ± 0.2	+ 0.2 ± 0.1	+ 0.1 ± 0.2 *
shortening vel (m/s)	+ 4.4 ± 1.8	+ 3.4 ± 2.2	+ 1.7 ± 1.9 ** °
lengthening vel (m/s)	+ 2.8 ± 1.7	+ 3.2 ± 1.8	+ 0.9 ± 2.0 * °°
PES (mm)	0	- 0.7 ± 1.0 *	+ 0.9 ± 1.2 * °°

*: $p<0.01$; **: $p<0.001$ v controls; °°: $p<0.01$; °°: $p<0.001$ Id-DCM v IS-DCM

Conclusion: Long axis electromechanical delay shortens and PES decreases in idiopathic DCM (similar to controls). Stress-induced ischaemic dysfunction includes increased electromechanical delay, exaggerated post-ejection shortening and impairment of total amplitude and long axis velocities. These differences may be used to confirm the presence of ischaemic aetiology in patients with DCM.

P434 Regional systolic function by Doppler tissue imaging in dilated cardiomyopathy; contribution for prediction of clinical outcome and prognosis

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Introduction: In dilated cardiomyopathy (DCM) NYHA class II-III, prognostic accuracy remains limited. The longitudinal component of left (LV) and right ventricular (RV) function seems important and may be studied by Doppler tissue imaging (DTI). The isovolumic and ejection systolic components may be also studied. We interrogated the relationship between regional LV, RV function and prognosis in DCM.
Methods: 42 pts with DCM were studied (age 53±14 years, EF 32±9%). VO2max was estimated within <1 month from echo study (ml/kg/min:18±6). Mean time from DCM diagnosis was 6±4.4 years and time elapsed from index echo 15±8 months. DTI profile was interrogated in 9 sites/pt: in the annulus(site 1), in the middle of the segment (site 3) and in the middle between sites 1 and 3 (site 2) of septal (IVS), lateral wall (LAT) for LV and RV free wall. Systolic phase consisted of two waves, an early-isovolumic (Siso) and a late one-ejection (Sez). Displacement was measured in the posterior mitral annulus (LATann) and tricuspid annulus (Rvann). 18 pts had cardiac events (CE: 3 death, decompensation/hospitalization, 3 transplant list, 12 NYHA III-IV), where 24 remained stable or improved NYHA class (nonCE).
Results: Group CE/nonCE had similar LVDD, EF, LATann, transmitral E, A, dec E. However group CE had lower: VO2max, Rvann, all R S indices, all IVS except 2Siso and 3Sez, all LAT except 2Siso, 3Siso, 3Sez. With receiver operating curve analysis (ROC) applied for prediction of outcome, the best discriminative parameters were as follows:

	cut of point: cm/sec	sens	spec	area under ROC	p
IV1Sez:	4.2	89	68	0.88	0.000
RV3Siso:	5.5	82	74	0.83	0.000
VO2max:	16	73	100	0.85	0.001
LAT1Siso:	2.5	71	80	0.79	0.002
IV3Siso:	3.6	73	60	0.71	0.037

LATann and Rvann had no contribution. The VO2max<14 as predictor of adverse outcome had sens=0.53, spec=0.94, pos.pred.v.=0.89, neg.pred.v.=0.70. When DTI data were considered in the presence of VO2max<14, then its negative predictive value was improved from 0.70 to 0.85, 0.92, 0.82, 0,82 with IV1Sez, RV3Siso, LAT1Siso, IV3Siso cut off points respectively.
Conclusions: Regional LV long axis and RV free wall interrogation by DTI provides a prognostic information which is independent from VO2max. Both isovolumic and ejection phase components by DTI provide incremental negative prognostic yield in the presence of low VO2max values.

P435 L-thyroxine replacement therapy improves left ventricular functions in subclinical hypothyroidism, as assessed by Doppler tissue imaging

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Aim: Subclinical hypotyroidism (SH) is usually an asymtomatic state associated with normal serum free thyroid hormones, but slightly elevated serum thyrotropin (TSH) levels. Doppler tissue imaging (DTI) is an objective method to quantify regional and global left ventricular (LV) functions through the assessment of myocardial velocity data. Several invasive or noninvasive diagnostic tools indicated a close correlation between LV functions and thyroid status, but limited data is available related to the effects of changes in thyroid status on DTI. The aim of the study was to evaluate the effects of L-thyroxine replacement therapy on LV functions in patients with SH by means of DTI.
Methods: Twenty patients with SH and 20 healthy subjects were included in the study. The diagnosis of SH was made based on elevated serum TSH >5.2mIU/L, with normal T4 and T3 levels. All subjects underwent standard M-mode, 2-D and Doppler echocardiography, as well as, DTI studies from septum and lateral wall. After echocardiographic assesment patients received L-thyroxine replacement therapy at a dose that could keep the serum TSH levels within normal range. After 6th month the echocardiographic and laboratory investigations were repeated.
Results: Patients with SH (2 male, 18 female; age 40.8±2.1yrs) were similar to controls with respect to age and sex characteristics (2 male, 18 female; age 39.3±2.3yrs) (p>0.05). The mean serum TSH, T4 and T3 levels of the SH patients before inclusion were 9.2±0.5mIU/L, 6.2±0.8ng/ml and 1.4±0.3ng/ml respectively. At baseline DTI studies indicated that SH patients had significantly lower lateral wall S velocity (p=0.001), lateral wall S time velocity integral (TVI) (p=0.001), lateral wall E velocity (p=0.009), lateral wall E TVI (p=0.01), septal S velocity (p=0.0001), septal S TVI (p=0.01), septal E velocity (p=0.008) and septal E TVI (p=0.007) values compared to controls. After a 6-month therapy with L-thyroxine DTI data showed significant increases in lateral wall S velocity (0.122±0.001 cm/sec to 0.145±0.001cm/sec, p=0.025), lateral wall S TVI (0.017±0.001cm to 0.023±0.001cm, p=0.001), septum E velocity (0.179±0.012cm/sec to 0.210±0.014cm/sec, p=0.021) and septum E TVI (0.018±0.001cm to 0.025±0.001cm, p=0.003) values in parallel with the significant improvement in ejection fraction (60.4±2.2% to 66.8±1.4%, p=0.039).
Conclusion: Patients with SH might have some functional cardiovascular abnormalities detected by DTI method despite the absence of clinical signs and symptoms. However, these findings can be reversible with L-thyroxine therapy.

P436 Specific tissue Doppler predictors of preserved systolic and diastolic left ventricular function after an acute anterior myocardial infarction

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Background: The degree of left ventricular (LV) dysfunction determines the outcome of patients suffering an acute anterior myocardial infarction (AAMI). Many recent studies have utilized tissue Doppler echocardiography (TDE) parameters in the assessment of LV long axis function.
Aim: We sought to investigate whether some variables easily obtained from pulsed wave TDE profiles of mitral annular corners would predict a relatively preserved LV global function traditionally assessed with ejection fraction (EF) and deceleration time (DT), within the acute phase of AAMI.
Methods: Included were 50 consecutive patients with a first AAMI. Standard echocardiography and TDE of mitral annulus were performed within 36 hours of admission. TDE velocity profiles were obtained by placing four sample volumes at septal, lateral, anterior and inferior corners of mitral annulus. Preserved LV function was defined as an EF > 40% together with a DT between 140 ms and 220 ms.
Results: With respect to the limits of EF and DT mentioned above, 16 (32%) patients had a relatively preserved LV global function. An inferior annular Sm of > 7.5 cm/s predicts preserved global LV function with a sensitivity of 81% and specificity of 71%. An anterior mitral annular Em of > 8cm/s had a sensitivity of 69% and specificity of 85%. Patients who had both an inferior Sm and anterior Em exceeding the limits above, such a combined index yielded a sensitivity of 69%, specificity of 94%, and an overall diagnostic accuracy of 86% – with only 5 false positive and 2 false negative results – for the estimation of a preserved LV global function.
Conclusion: The parameters derived from TDE profiles of inferior and anterior mitral annulus corners provide valuable information to predict a preserved global LV function during the early period of AAMI. When the difficulty and operator dependency of particularly measuring EF in asymmetrically contracting ventricles to consider, these two parameters, which could easily, quickly, and reliably be measured, would be helpful to predict a well-preserved global ventricular function in clinical setting.

P437 Prediction of contractile function recovery by tissue Doppler imaging: a usefulness of myocardial pre-ejection and postsystolic velocities

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So far, a simple and accurate method for assessing viability is missing. In experimental studies, both myocardial pre-ejection velocities (PEV) and postsystolic shortening (PSS) seem to correlate with the extent of the viable myocardium.
Aim: To compare the predictive value of the resting pattern of PEV and PSS to predict recovery of contractile function in patients (pts) with myocardial infarction.
Methods: Fourteen pts with one totally occluded coronary artery (LAD 10, LCx 1, RCA 3) and severe wall motion abnormalities in the region at risk were selected. Longitudinal myocardial velocities were recorded at rest by transthoracic pulsed wave tissue Doppler (TDI) within 24 hours after revascularization. Global and regional left ventricular (LV) function was assessed by LV angiography at baseline and two months after revascularization. Recovery of contractile function was defined as an increase in segment shortening by more than 10% at follow-up angiography.
Results: TDI signals in regions at risk were obtained in all pts regardless the quality of two-dimensional images. A total number of 49 dysfunctional segments were analyzed of which 34 recovered and 15 did not. Table 1 shows accuracy of the presence of +PEV, PSS and their combination to predict recovery at follow-up. The combination of both parameters significantly reduced the number of false positive results and thus increased specificity and positive predictive value as compared to both indices alone.

	Sensitivity	Specificity	PPV	NPV	Accuracy
+PEV	97	67	87	91	88
PSS	74	53	78	47	67
+PEV and PSS	97	80	92	92	92

Conclusions: The resting pattern of PEV and PSS in the infarct-related area may predict the recovery of regional function within hours after reperfusion. The combination of both parameters is superior to either parameter alone.

P438 Post systolic thickening can be a marker of myocardial viability

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We wanted to determine the myocardial viability after acute myocardial infarction by tissue pulsed Doppler echocardiography (TDE) measuring the post systolic thickening (PST) of the ischemic myocardial segment. The tissue Doppler echocardiographic data were compared to the myocardial scintigraphic measurements.
We examined 32 patients with acute myocardial infarction and 35 healthy subjects. In the patients group the ischemic wall motion abnormalities were determined by second harmonic 2DE. TDE was applied in all ischemic myocardial segments according to the 16 segments model. The segment was respected as viable if the velocity wave of the post systolic thickening exceeded more than 30% of the amplitude of the systolic velocity wave. Examinations were performed at resting conditions. In the healthy subjects all 16 segments were examined by TDE. Between 24-48 hours later rest-redistribution Tl-201 myocardial scintigraphy was done in each case The reversible myocardial perfusion defect indicated the myocardial viability as hibernating myocardium.
The post systolic thickening can be detected as a velocity wave during the isovolumic relaxation period just before the mitral valve opening. We found it very seldom in the healthy population. We examined 560 healthy myocardial segments and we found PST in 15 segments (2.6%) mostly in the basal region (9 segments 1.6%). In the patient group 161 ischemic segments were observed. Out of them the Tl-201 scintigraphy in 123 cases while the PST in 114 cases indicated myocardial viability. The following statistical data show the accomplishing ability of the PST determing by TDE in the detection of myocardial viability compared to Tl-201 myocardial scintigraphy: sensitivity: 82.1%, specificity: 65.7%, positive predictive value: 88.5%, negative predictive value: 53.2%, accuracy: 78.2%.
Conclusions: The post systolic thickening of the myocardial wall can idicate the myocardial viability. Its positive predictive value highly significantly predicts the viability of the ischemic myocardium. It can be detected easily by TDE and may be very useful even in resting condition.

P439 Clinical significance of postsystolic thickening detected by Doppler myocardial imaging in patients with myocardial infarction

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Background: Although it is well known that postsystolic thickening of ischemic segment (PST) can be detected by Doppler myocardial imaging (DMI) in acute ischemic model, the prevalence and clinical significance in patients with myocardial infarction (MI) has not been seriously investigated.
Methods: Among patients who underwent routine dobutamine stress echocardiography (DSE) for detection of peri-infarction viability or ischemia, those with MI at the left anterior descending artery territory were selected. Myocardial velocity data of interventricular septum at apical 4 chamber view and those of inferior wall at 2 chamber view were retrospectively analysed. DMI was routinely recorded in each stage of DSE, and (+) PST was defined as positive velocity > 2 cm/sec after peak systolic velocity at rest or more than 2 times increase of positive velocity at low dose dobutamine infusion compared to the value at rest.
Results: Total 20 patients (16 male, 59.8±12.7 years) were enrolled for this study and DMI data could be analysed in 37 segments (93%). Mean wall motion score index (WMSI) and peak systolic velocity (PSV) in ischemic segments were 2.1±0.6 and 1.4±1.3 cm/sec, respectively. PST was observed in 20 segments (54%) including 3 segments showing PST only in low dose dobutamine stage, and 19 segments (51%) showed peri-infarction viability or ischemia during DSE. There was no significant difference of baseline WMSI (2.1±0.3 vs 2.1±0.5, p=0.76) or PSV (1.1±1.1 vs 1.9±2.0 cm/sec, p=0.05) between segments with PST and those without. Peri-infarction ischemia or viability was more frequently observed in segments with PST compared to those without (85% vs 18%, $p<0.05$). The sensitivity and specificity of PST for prediction of peri-infarction ischemia or viability was 85% and 82%, respectively.
Conclusions: PST is not infrequently detected by DMI in chronic ischemic segments, and is closely related with positive DSE for peri-infarction ischemia or viability. Diagnostic accuracy of DSE for detection of peri-infarction viability or ischemia can be enhanced by objective analysis of velocity data obtained by DMI.

P440 Myocardial pre-ejection velocities assessment by tissue Doppler imaging: a new predictor of recovery of contractile function in humans

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Normal pattern of myocardial pre-ejection velocities (PEV) consists of positive (+) and negative (-) PEV reflecting a brief inward and outward motion of the myocardium during isovolumic contraction (i.e. occurring before the opening of the aortic valve).
Aim: To investigate the relationship between the resting pattern of PEV and the recovery of contractile function upon recanalization of a totally occluded coronary artery in humans.
Methods: Accordingly, 14 patients (pts) with acute coronary syndrome and severe wall motion abnormalities were selected. Pulsed wave tissue Doppler (TDI) using transthoracic approach was performed within 24 hours after revascularization (LAD 10, LCx 1, RCA 3). Longitudinal PEV in dysfunctional myocardial segments were recorded at rest in apical views. Global and regional left ventricular (LV) function was assessed by LV angiography at baseline and two months after revascularization. Recovery of contractile function was defined as an increase in segment shortening by more than 10% at follow-up angiography.
Results: The registration of PEV was possible in all pts despite poor image quality of two-dimensional images in 14% of them. The sampling of all dysfunctional segments lasted on the average 10 min per pts. Of 49 dysfunctional segments analyzed, 34 segments recovered while 15 segments did not. A +PEV was present in 33/34 segments that finally recovered and in 5/15 segments that did not. Any +PEV was absent in 10/15 segments that did not show recovery and in 1/34 segments that did. Accordingly, sensitivity, specificity, and diagnostic accuracy of the presence of +PEV to predict regional recovery were 97%, 67%, and 88%, respectively. In addition, amplitude of +PEV significantly correlated with the change of segment shortening during follow-up ($r=0.55$, $p < 0.05$).
Conclusions: An assessment of PEV by pulsed wave TDI is a promising, simple and fast method not requiring any form of stress to predict recovery of contractile function upon coronary revascularization.

P441 Tissue motion imaging – a new and quicker way to assess left ventricular function by ultrasound

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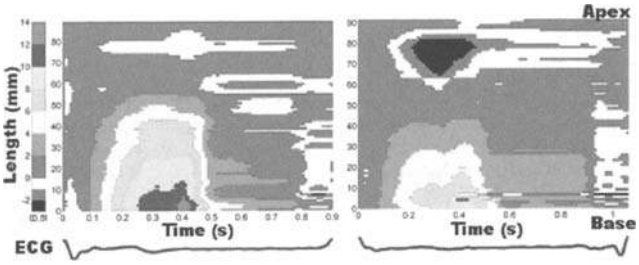
Previous ultrasound imaging techniques of the left ventricular function such as tissue velocity imaging and strain rate imaging all have the limitation that they only present one parameter and that they are mainly suitable for the assessment of systolic function.

In the present study we have investigated the visualization of tissue motion which is the result of an integration over time of myocardial velocities extracted on a curved M-mode. By applying a color-map to this information one gets the Tissue Motion Image (TMI).

TMI was applied to two age matched groups of ten individuals who all underwent a standard dobutamine-atropine stress test, the first group consisting of normals, the second of patients with coronary artery disease. The maximum motion in the normals was 13.8±4.4 mm and 14.0±5.4 mm at rest and peak stress, respectively. In the patients maximum motion was 11.2±7.2 mm and 10.8±7.6 mm at rest and peak stress, respectively (values given in mean±1.96SD). The motion of the patients was significantly lower than that of the normals. This is directly reflected by and rapidly interpreted from the images as different colors for the peak values. By TMI one can also typically see reduced diastolic function as a temporally more smeared pattern and dyskinesias as black spots in systole at a glance. In the figure to the right dyskinesia is seen apically.



Healthy (left) and dyskinetic (right).

Knowing that the temporal derivative of this image is the velocity, and that another differentiation gives the acceleration and retardation, both of these are easily interpreted from the TMI. The spatial derivative is the strain, so one can even assess regional strain from TMI, hence one can quickly get a better qualitative impression of regional myocardial function than by previous visualization techniques.

P442 Usefulness of a new automatic segmental motion analysis system in the diagnosis of multivessel disease in anterior acute myocardial infarction

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It has been previously described that absence of compensatory hyperkinesia in patients with acute myocardial infarction (AMI) suggests the presence of multivessel disease (MVD). However, since the assessment of myocardial contractility is subjective, the diagnostic usefulness of this characteristic is limited. The objective of the study was to evuate the differences in myocardial wall thickness between AMI patients with or without MVD using a new method of cuantifying automatically and in real-time.

The study population is comprised by 14 patients with anterior AMI within 3 days after admission. These patients underwent cardiac catheterization and echocardiographic study using a commercially available equipment (Aloka SSD 870, Tokyo) able to automatically analyse the myocardial segmental thickness in real-time. The myocardial thickness at 80 and 120 msec. from the R wave, and time to maximum thickness were measured in the lateral wall. These parameters were compared between patients with and without MVD.

Results: Mean age was 57±8 years, and 11 (79%) were male. Out of the 14 patients, 8 (57%) had a single-vessel disease (left anterior descending coronary artery), whereas the remaining 6 (43%) had MVD. The comparison between patients with and without MVD is shown in the table:

Single- vs. Multi-vessel disease

	Single-vessel	Multi-vessel	p
80 msec thickenning (%)	8.3±4.3	7.5±3.8	NS
120 msec thickenning (%)	32.1±6.3	16.3±4.1	<0.05
Time to peak (msec)	286±24	278±27	NS

Conclusion: In patients with anterior AMI, those with MVD had an impaired regional wall thickenning at 120 msec. in the contralateral wall, as can be measured by a regional wall thickenning quantification system.

P443 A novel modality to evaluate left ventricular function: tissue tracking

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Background: Tissue tracking imaging allows rapid assessment in apical views of the systolic baso-apical displacement for each myocardial segment by a graded color display.

Methods: To assess the ability of Tissue Tracking for assessment of LV function by determination of the systolic mitral annular displacement (MAD), we studied 90 patients (69 male, age 60.4±10.1years) with different LV function, including 25 subjects with normal LV function, 25 patients with homogenous depression of LV function due to cardiomyopathy and 40 patients with prior myocardial infarction (MI) and regional depression of myocardial contractility. The systolic MAD was determined by Tissue Tracking and M-mode echocardiogaphy. The apical four chamber, three chamber and two chamber views were used to determine the MAD of 6 sites. LV ejection fraction (LVEF) was determined by 2-D echocardiography using Simposon's rule in all patients and contrast cineangiography in 27 patients.

Results: Tissue Tracking was possible in all 90 patients. In 50 patients, including 25 patients with normal LV function and 25 patients with homogenous depression of LV function, mean MAD measured from 6 sites of the mitral annulus correlated closely with MAD determined by M-mode ($r=0.99$, $p<0.001$) and with the LV ejection fraction determined by 2D echocardiography ($r=0.97$, $p<0.001$). Using a cut-off value of 4.8mm for the MAD determined by Tissue Tracking, LV ejection fraction≤30% can be predicted with a sensitivity of 98% and a specificity of 78%. In patients with prior MI correlation between the mean MAD measured by Tissue Tracking and the LV ejection fraction determined by 2D echocardiography was lower($r=0.87$,$P<0.001$).

Conclusions: Systolic MAD determined by Tissue Tracking correlates closely with MAD determined by M-mode and with LV ejection fraction determined by 2D echocardiography. Thus, MAD determined by Tissue Tracking provides a simple, rapid, and noninvasive tool to assess global LV function.

P444 Myocardial velocity-displacement loops constructed from tissue Doppler data in patients with hyperthyroidism

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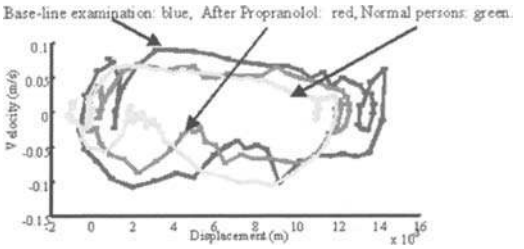
Objectives: Tissue Velocity Imaging (TVI) is an off-line program with the advantage of extraction myocardial velocity from color-coded Doppler information. Myocardial velocities can be used in calculation of related variables such as displacement (Distance). Plotting myocardial velocity against displacement will construct the myocardial loops that may represent the instantaneous work done by the heart. Thyroid hormones have marked chrono- and inotropic effects on the heart. These effects may be due to enhanced response to catecholamines, and may be partially or totally reversed by beta-blockade. 16 thyrotoxic patients, mean age 38±9 years, with high levels of plasma free tri-iodothyronine (fT3) 30±5 pmol/L, and no previous heart diseases, were examined before and 2 hours after giving Propranolol 40 mg per Os. 36 age-matched healthy individuals served as a control. Velocities were acquired in the basal septum and integrated over time to calculate the displacement. The loops were constructed by plotting the velocity at one time instant with the displacement at the same instant (Diagram 1). The area inside the loop represents the amount of longitudinal work done by the heart to move the basal part of the septum towards the apex with a certain acceleration.



Velocity - displacement loop

Results: The basal longitudinal velocity of the septum were consistently higher in thyrotoxic patients at base-line examination compared to control group ($p<0.001$). Propranolol reduced the longitudinal systolic velocity from 8.5±1.5 to 4.5±1.2 cm/sec ($p<0.001$). Propranolol reduced significantly the area inside loops at base line examination by 40% ($p<0.001$).
Conclusion: Velocity-displacements loops can be used in clinical assessment and demonstration of the inotropic effects of thyroid hormones in thyrotoxic patients.

P445 Importance of the physiologic immobility of the cardiac apex: tissue Doppler assessment during off-pump coronary surgery

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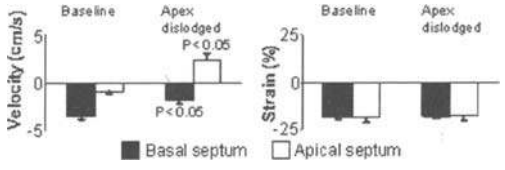
Background: It is not clearly understood why apex is hardly moving while longitudinal ventricular motion is directed towards apex during systole. This was investigated by tissue Doppler assessment of septal motion before and during exposure of the heart inherent in off-pump coronary bypass surgery.
Methods: Longitudinal systolic velocities of septum were measured by transoesophageal echocardiography in seven patients during the operation, including when apex was dislodged from the pericardial sac. This is part of the regular proce-dure before anastomosing left internal mammary artery to the left anterior descending artery. Invasive haemodynamic measures were monitored throughout the operation.
Results: Basal septal velocity and the normally lower velocity of apical septum were both directed towards apex before thoracotomy (Fig). No definite change occurred after pericardiotomy. However, dislodging apex from the pericardial sac caused a shift of apical septal motion towards the base of the heart, along with reduced basal motion towards the apex (Fig.). Strain Doppler, reflecting myocardial shortening, remained unchanged in both septal segments. Heart rate increased (from 54 ± 6 (mean ± SEM) to 73 ± 6 beats/ min, $p<0.05$) and stroke volume tended to decrease (from 84 ±12 to 71 ± 10 ml, ns), without any other haemodynamic changes.



Conclusions: Dislodging apex from the pericardial sac caused a conspicuous change of longitudinal septal motion as shown by tissue Doppler. Concomitantly, the haemodynamic findings indicated reduced ventricular performance despite normal myocardial shortening. Thus, the normal ventricular motion towards apex, along with apical immobility, seems physiologically important and dependent on apex being situated within the pericardial sac.

P446 Changes in left ventricular morphology of world-class professional bicyclists between 1995 and 1998

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Illicit use of drugs aiming at improving performance (erythropoietin, growth hormone, androgenic steroids), has disturbed popular cyclist competitions during last years, especially the "Tour de France". We hypothesis that the magnitude of these practices could be investigate by the detection of changes in left ventricular (LV) morphology.
Methods: Two days before the beginning of the "Tour de France", the same investigator obtained in very similar conditions, M-mode LV tracings in 149 bicyclists (1995) and in 139 bicyclists (1998). 37 athletes were included in both studies. All of the readings were taken from anonymous tracings by a single investigator. Final result was obtained as the mean of 3 measurements for diastolic LV diameter (LVIDd), septal thickness (IVST) and posterior wall (PWT).
Results: 1995 and 1998 athletes were similar for age (28 years), size (body surface area: 1.89 m^2), and blood pressure (120/66 mmHg). Participants in the 1998 race had larger LV cavities and thinner walls than those of the 1995 participants(all $p<0.001$):
1995: LVIDd = 59.2±3.7 mm, IVST = 11.6±1.3 mm, PWT = 10.3±1.1 mm
1998: LVIDd = 60.8±4.3 mm, IVST = 10.6±1.2 mm, PWT = 9.8±0.7 mm
A comparable difference was found in the subgroup of 37 who participated in both races(all $p<0.001$):
1995: LVIDd = 58.3±4.8 mm, IVST = 11.8±1.2 mm, PWT = 10.6±1.0 mm
1998: LVIDd = 60.3±4.2 mm, IVST = 10.8±1.2 mm, PWT = 9.9±0.8 mm
In the 1995 population, one cyclist had a LVIDd > 70 mm versus 3 in the 1998 population (one cyclist is common to the two populations).
Conclusion: Our data show that it is possible to quantify cardiac changes in trained athletes over a short period of time. The 2000-2001 law suits have confirmed the large-scale use of EPO and others drugs in cyclists. Since physical training technology is unlikely to change over a few year interval, this suggest that the observed modifications of LV geometry could be, at least in part, due to "pharmacological training" rather than to physical training.

P447 The effect of gestational hypertension on left ventricular geometry

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Objectives: Heart rate, stroke volume, cardiac output and left ventricular mass increases during pregnancy while peripheral vascular resistance decreases. Gestational hypertension (GHT) which is noted in some pregnancies during the third trimester is considered as a temporary condition. Its effects on left ventricular geometry (LVG) is not known. In this study we aimed to assess the effects of this acute pressure overload in GHT on the LVG.
Matherials and Methods: Fortythree pregnant women (mean age 28.7±8.9 years) with gestational hypertension were included in the study (Group A). Blood pressure levels over >140/90 mmHg were considered as GHT in this group. Fiftysix pregnant women (mean age 25.7±5.7 years) with normal blood pressures formed the control group (Group B). Transthoracic echocardiographic evaluation was performed on left lateral decubital position for all women before delivery. Left ventricle (LV) end-systolic (ES) and end-diastolic (ED) diameters, LV septal and posterior wall thickness were measured and LV mass index (MI) and relative wall thickness (RWT) were calculated using Devereux and Ganau formulas. LVG was defined as normal (N), concentric hypertrophic (CH), eccentric hypertrophic (EH) and concentric remodeling (CR).
Results: LVMI and RWT were 138±13.8 g/m^2 and 0.46±0.09 and 117±15 g/m^2 and 0.4±0.03 in Group A and Group B, respectively ($p=0.01$, $p=0.03$). LVG was %38.9 N, %19.4 EH, %14 CH, %27.7 CR in hypertensive pregnants and it was %78.6 N, %7 EH, %5.4 CH, %9 CR in normotensive pregnants ($p<0.001$).
Conclusion: These findings suggest that LVMI and RWT is greater in GHT compared to normotensive pregnants. Most frequently observed abnormal geometric pattern is EH and CR

P448 Effect of acute intravascular volume and arterial pressure changes on left ventricular function during haemodialysis

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Deterioration of left ventricular (LV) diastolic function has been causally related to hypotensive episodes during hemodialysis (HD).The effect of intravacsular volume and arterial pressure reduction on LV function of patients without hypotensive episodes during HD has not been adequately studied.

Methods: We studied 23 patients on HD for 48±35 months, with mean age 50±12 years, body mass index 24±4kg/m^2 and mean fluid retention between HD sessions 2.2±1.1 kgr using 2D and Doppler echocardiography before and after HD. We measured:a)end-diastolic (LVED) and end-systolic LV diameters,left atrial diameter(LA) and fraction shortening (FS) b)isovolumic relaxation (IVRT) and contraction (ICT) time, deceleration time (DT), E and A waves of the mitral inflow and ejection time (ET) of the LV outflow velocity. The following indices were calculated:E/A ratio, myocardial performance index (MPI) using the formula (IVRT+ICT)/ET, mean arterial pressure (MAP), the % reduction of MAP and the reduction of intravascular volume (ultrafiltration volume-UFV) after HD.

Results: All patients had systolic arterial pressure >90mmHg and normal FS before and after HD, while they demonstrated a restrictive LV diastolic filling before HD (table). MAP, LVED, LA, E wave, E/A, decreased while IVRT increased after HD ($p<0.01$). After HD,low MPI values (normal range<0.44) were related to greater UFV loss ($r=0.53$, $p<0.01$) and greater % reduction of MAP ($r=0.62$, $p<0.01$). Conversely, abnormal MPI values were related to high MAP after HD ($r=0,44$, $p<0.01$). Increased UFV loss was related to greater % increase of IVRT ($r=0.43$, $p<0.01$) and % decrease of E/A ($r=0.40$, $p<0.01$) after HD. Patients with UFV loss >3kg (7/23) had lower MPI (0.47±0.2 vs 0.84±0.3, $p<0.01$) and greater %increase of IVRT and %reduction of E/A ($p<0.01$) than those with <3kgr.

Hemodialysis	MAP (mmHg)	LVED (mm)	LA (mm)	E (m/s)	E/A	IVRT (ms)	ET (ms)
Before	100±15	52±6	43±5	0.86±0.2	1.2±0.2	64±14	298±85
After	86±12	48±6	39±5	0.61±0.2	0.8±0.2	89±19	241±54
p	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

Conclusion: Fluid retention between HD sessions leads to restrictive LV diastolic filling as shown by an E/A>1 and a short IVRT in patients before HD. Reduction of the excess intravascular volume after HD normalises the MAP and thus, improves LV performance

P449 Tissue Doppler data imply that artifacts in conductance measurements in the left ventricle during isovolumic phases are due to tissue movements

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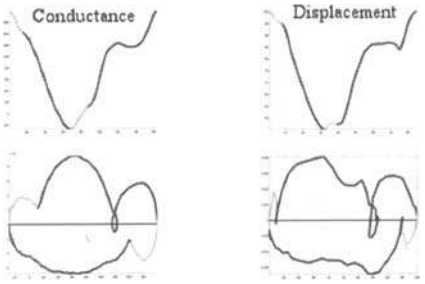
Objective: Volume measured by the conductance method often decrease during isovolumic contraction (IVCT) and increase during isovolumic relaxation time (IVRT). We evaluated if movements in the muscle of the left ventricle (LV) was correlated to changes in LV conductance during IVCT and IVRT.

Methods: Using ultrasound tissue doppler 18 healthy normal men were studied. Longitudinal velocities were measured in the LV septum and lateral wall. Velocities were integrated to displacement, i.e. movement in LV wall. These displacement curves were compared to the volume curves, measured with the Biometrics conductance catheter on pigs undergoing open-chest surgery with intact pericardium.

Results: The curves from the two types of measurements were similar, with almost identical appearance during IVCT and IVRT.

Conclusion: Movements in the cardiac wall during IVCT and IVRT may influence measured volume by the conductance method.



Conductance to the left, displacement to the right. Top figures are data plotted against time. Below the same data are plotted against their own first derivative (flow and velocity, respectively).

CORONARY CIRCULATION

P450 Phasic coronary blood flow pattern and flow reserve in the atrium: regulation of the left atrial myocardial perfusion

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Background: Due to the limitations of the methods used until now for assessing myocardial perfusion in the small mass of atrial tissue, human atrial myocardial perfusion data is lacking.

Objectives: The purpose of this study was to assess rest and stress atrial coronary blood flow and flow reserve.

Methods: Ten patients with suitable coronary anatomy underwent coronary blood flow velocity (APV) measurements, using a 0.014 inch Doppler guidewire in the proximal left circumflex coronary artery (LCx) and in the left atrial circumflex branch (LACB), at baseline (b) and after adenosine (h) administration. Coronary flow reserve was calculated as h-APV/b-APV. All measurements were done at resting heart rate, at 100 bpm and 120 bpm.

Results: As shown in the table, there was a disproportionate increase in baseline coronary blood flow between LACB and LCx during the two levels of stress (significant interaction $p<0.001$) but no significant differences in coronary flow reserve.

	LCx			LACB		
	Rest	100 bpm	120 bpm	Rest	100 bpm	120 bpm
b-APV cm/sec	16.8 + 5.8	18.9 ± 5.6	20.1 ± 5.7	17.6 ± 5.8	23.6 ±8.1	28.2 ± 7.9
h-APV cm/sec	47.2 ± 17.7	46.7 ± 17.4	44.6 ± 16.2	46.9 ± 14.9	51.9 ± 17.2	52.3 ± 15.9
CFR	2.9 ± 0.7	2.5 ± 0.7	2.3 ± 0.6	2.7 ± 0.6	2.2 ± 0.3	1.9 ± 0.3

Conclusions: Although atrial and ventricular coronary flow reserve show no significant differences at rest and two levels of stress, the disproportionate increase in atrial blood flow during stress indicates a peculiarity of atrial perfusion regulation leading to early exhaustion of vasodilator reserve.

P451 Favorable effect of phentolamine on coronary vasomotion during dobutamine stress testing in patients with coronary artery disease

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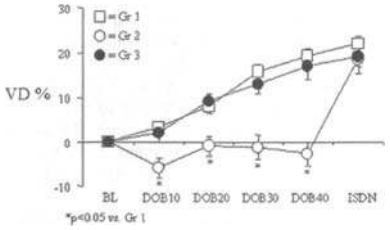
Coronary artery disease (CAD) is associated with enhanced alpha-adrenergic vasomotor tone. Dobutamine (DOB), a drug currently used to detect CAD, is an alpha- and beta-adrenergic agonist.

Aim: To explore the contribution of alpha-adrenergic component in the vasomotor response to DOB in patients with CAD.

Methods: Vessel diameter (VD, %) was assessed at baseline (BL), during IV DOB (10, 20, 30, 40 μg/kg^{-1}.min^{-1}) and after IC isosorbide dinitrate (ISDN, 2 mg) in 85 coronary segments of 19 subjects with normal coronaries (Gr 1) and in 36 coronary segments of 12 patients with tight stenoses (Gr 2). A IC bolus of phentolamine (PHENTO, 12 μg/kg), a non-selective alpha-adrenergic antagonist, was followed by the above protocol in 48 coronary segments of 10 patients with tight stenoses (Gr 3).

Results: Angiographic severity of coronary stenoses was similar in Gr 2 and 3. A similar rate pressure product increase during DOB was observed in all three groups. In Gr 1, DOB induced a dose-related increase in VD. In Gr 2, DOB induced no significant vasomotion. Yet, when atherosclerotic vessels were pretreated by PHENTO (Gr 3), a similar vasodilation was observed than in normals during DOB. ISDN resulted in similar vasodilation in all three groups (figure).



Conclusion: In patients with CAD, PHENTO restores DOB-induced vasorelaxation suggesting an overriding of the beta- by the alpha-adrenergic component in CAD.

P452 Parathyroid-hormone related peptide increases coronary flow in a nitric oxide independent way

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Background: Parathyroid hormone-related peptide (PTHrP) is a peptide hormone that is produced and released from the coronary endothelium. It acts as a dilating factor and therefore is able to increase the coronary flow. It is, however, not clear, whether this dilating effect is nitric oxide (NO)- and therefore endothelium-dependent or not. The local concentration of PTHrP is increased at the end of ischemia. Therefore, the early phase of reperfusion is performed in the presence of high endogenously released PTHrP. The answer of the underlying mechanism of the PTHrP effect allows a prognosis about the ability of PTHrP to increase coronary flow in the presence of post-ischemic endothelial dysfunction. Methods: We determined coronary flow in pressure-constant perfused rat hearts (55 mm Hg) which were paced at 3 Hz. Ischemia was performed by a 30 minute no-flow periode. The pre-ischemic apparent coronary flow was 6.2±1.2 ml/g heart weigth which was reduced to a post-ischemic value of 4.7±1.3 ml/g. Experiments were performed in presense of synthetic PTHrP(1-36) (100 nM, EC50: 0.5 nM), the endothelium-dependent vasodilator bradykinin (10 μM), the NO-donor spermine-NONOate (100 nM), and L-nitro-arginin (L-NA, 100 nM), which was used to inhibit NO production by the endothlium. In pre-ischemic experiments, hearts were preconstricted by addition of phenylephrine (10 μM). Results: Under basal conditions, PTHrP increased coronary flow by 19±9%, bradykinin by 37±7%, and spermine-NONOate by 15±8% (each n=4, $p<0.05$ vs. control). In presence of L-NA basal coronary flow was reduced to 3.9±1.2 ml/g, but PTHrP still increased coronary flow by 16±9%. In contrast, bradykinin did not shown an effect in presence of L-NA. Post-ischemically, spermine-NONOate and PTHrP were still able to increase coronary flow by 19±9% and 21±7%, respectively. However, bradykinin did not show any effect on coronary flow during the post-ischemic reperfusion.
Conclusion: PTHrP increased coronary flow in a NO- and endothelium-independent way. Therefore, PTHrP-induced coronary flow is able to compensate for post-ischemic endothelial dysfunction in the heart. PTHrP seems to be a relevant endogenously released factor contributing to post-ischemic recovery.

P453 Endothelin A receptor antagonism promotes decreased vasodilation but has no differential effect on coronary compliance in hypertensive patients

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Endothelin (ET) antagonism causes greater vasodilation in forearm vessels in hypertensive (HT) compared to normotensive (NT) patients. We examined whether there is a differential effect of ETA antagonism on vasodilation and coronary artery compliance in HT compared to NT patients.
Methods: We examined atherosclerotic non-stenotic arteries from 18 non-diabetic, 10 NT and 8 HT patients, before and after intracoronary infusion of BQ-123, an ETA receptor antagonist. The systolic and diastolic artery lumen area (DA) in the proximal segment was measured using an IVUS catheter.

		Baseline	After BQ-123	F	p
DA, mm^2	NT	8.9±2.9	10.8±3.0*	3.98	0.05
	HT	10.6±4.6	10.8±4.0		
beta	NT	1.52±0.63	1.41±0.73	0.86	0.37
	HT	1.80±0.66	1.46±0.58		

*: $p<0.05$ vs. baseline; â: stiffness index. Systolic blood pressure decreased only in HT patients ($F=5.44$, $p=0.03$).

Conclusion: ETA antagonism causes decreased vasodilation but has no differential effect on coronary artery compliance in HT patients.

P454 Direct assessment of the mechanism of coronary steal in chronic total coronary occlusions

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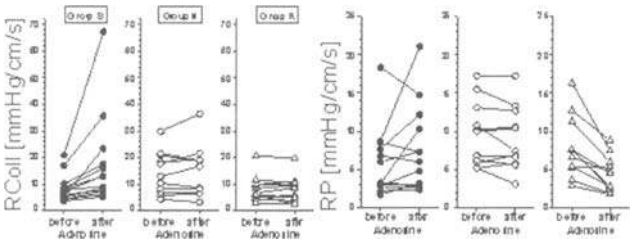
Background: Coronary steal can occur in collateral-dependent myocardium during pharmacologically induced vasodilation. This study assessed coronary steal invasively in chonic total coronary occlusions (TCO) to determine the underlying hemodynamic changes of the collateral circulation.
Methods: In 35 consecutive patients with a PTCA of a TCO (>4 weeks duration), a probing catheter was advanced distal to the occlusion to allow the assessment of coronary flow velocity (APV) by a Doppler wire, and distal pressure (PD) by a pressure wire in the collateral-dependent vascular bed. Collateral (RColl) and peripheral (RP) resistance indexes were calculated. These parameters were again obtained during intravenous adenosine (140 ?g/kg/min) and compared with baseline.
Results: APV decreased during adenosine in 13 patients (39%) representing coronary steal (group S), it increased in 11 patients indicating a collateral flow reserve >1 (group R), and no change occurred in 11 patients (group N). There were no clinical and angiographic differences between these groups. With steal RColl significantly increased, and RP remained unchanged, whereas in group R RP decreased and RColl remained unchanged (see Figure). In group N without changes during adenosine, collateral function was less developed with a high RColl.



Resistance changes during adenosin.

Conclusions: Coronary steal is observed in about one third of TCOs, and is associated with specific hemodynamic changes of RColl and RP. These in vivo observations were in accordance with the collateral network model to explain coronary steal. Steal occurred only in a well-developed collateral system, but there were no clinical parameters to predict its incidence.

P455 Limitations of medical therapy in patients with pure coronary spastic angina

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Objectives: To assess the efficacy of medication in pure coronary spastic angina, 71 consecutive patients (55 men, mean age of 63,10 years) with this diagnosis who had undergone coronary arteriography in hospital with a follow-up of at least 2 year were studied.
Methods and Results: All 71 patients without significant organic stenosis were treated with long acting calcium antagonists. The disappearance of chest pain attacks under medical therapy was observed in 27 (38%) patients, whereas the remainig 44 (62%) patients had chest pain attacks. Especially, 30 patients had more than 1 attack/month irrespective of the administration of calcium antagonists or isosorbide dinitrate. Medical treatment showed a good response in female patients (63% vs. 31%, $p<0.05$) and those with ST segment elevation during selective spasm provocation tests (63% vs. 30%, $p<0.05$). In contrast, patients with a longer history of chest pain attacks before admission and those with diffuse spasms (77% vs. 34%, $p<0.01$) had a poor response to medical treatment. In this study, neither sudden death nor acute myocardial infarction was observed during follow-up periods.
Conclusions: Limitations of medical therapy, including long acting calcium antagonists, were observed in 30 (42%) of 71 patients with pure coronary spastic angina. Medical treatment was effective in only 38% of patients with pure coronary spastic angina in Japan.

P456 Induction of coronary artery spasm by two pharmacologic agents: Comparison between intracoronary injection of acetylcholine and ergonovine

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This study examined whether or not intracoronary injection of acetylcholine (ACh) was similar to intracoronary administration of ergonovine (ER) for the induction of coronary artery spasm. We performed selective intracoronary administration of both ER and ACh in the same 171 patients (106 men, 62}10 years) with <50% stenosis. Under no medication, ACh was injected first in incremental doses of 20-100 mg. Ten minutes later, ER was administered in total doses of 40-64 mg. Positive spasm was defined as > 99% luminal narrowing. Coronary spasms were induced by either pharmacologic agents in 134 vessels from 70 patients. In the overall results, no difference was existed in the incidence of provoked spasm between the 2 agents (ACh: 33% vs. ER: 32%, ns). However, ER provoked more focal spasms, whereas ACh provoked more diffuse spasms. Seventy-four (56%) of all 134 vessels had coronary spasms on the same coronary arteries. Coincidence of both provoked spasms and spasm configuration on the same coronary artery was observed in only 16%(22/134). Coincidence of this study was 94% of all vessels, whereas the remaining 6% of vessels were different each other. Non-coincidence rate of RCA was significantly higher than that of LCA (9% vs. 4%, $p<0.01$). In conclusions, there is no difference between ACh and ER as a spasm provocation test. We recommend the supplementary use of these two pharmacologic agents for the induction of CAS in the cardiac laboratory, if available.

P457 Elevated high-sensivity C-reactive protein levels in patients with coronary spasm

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Background: Elevated high-sensivity C-Reactive Protein(hs-CRP) levels, an exquisitely sensitive objective marker of inflammation, are associated with restenosis, impaired endthelial vasoreactivity, and unfavorable prognosis in patients with coronary artery disease. However, the relation between elevated inflammatory markers and coronary spasm has not been documented. Accordingly, the aim of our study was to assess whether higher levels of hs-CRP could be found in patients with coronary spasm compared with those without coronary spasm.
Methods: The study group consisted of 38 consecutive patients (23 men and 15 women; mean age 60+12 years) undergoing coronary angiography for evaluation of vasospastic angina. Coronary spasm was defined as total or subtotal occlusion of the epicardial coronary arteries after the intracoronary injection of ergonovine. Patients were classified into 2 groups on the basis of coronary; 11 patients with coronary spasm, 27 patients no coronary spasm. All patients had no significant organic stenosis angiographically and free of noncardiac reasons causing increased hs-CRP levels. Blood samples (Total cholesterol, LDL-cholesterol, HDLcholesterol, Triglyceride, HbA1c, hs-CRP) were collected at the time of coronary angiography.
Results: There were no significant differences between 2 groups in age, sex, and incidence of major coronary risk factors. Patients with coronary spasm had significantly higher levels of hs-CRP than those without coronary spasm (1.56+1.26 mg/L vs 0.57+0.44 mg/L, $p < 0.01$).
Conclusion: Elevated hs-CRP levels were verified in patients with coronary spasm, indicating that inflammatory process was associated with coronary spasm.

P458 Nifedipine improves endothelial function and decreases vascular inflammation in coronary circulation: studies on patients with angina pectoris

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Objective: Ischemic heart disease is associated with endothelial dysfunction and atherosclerosis of the coronary arteries. The present study was designed to determine whether calcium channel blockers improve endothelium-dependent coronary vasomotion in patients with angina pectoris.
Methods: Fifteen male patients (mean age 65±2 years) with stable angina pectoris who underwent elective percutaneous transluminal coronary angioplasty (PTCA) were enrolled. Following routine PTCA, increasing doses of acetylcholine (3, 10, 30 μg/min for 3min) and then isosorbide dinitrate (ISDN; 2mg/min for 1min) were infused into the study coronary artery. Changes in the coronary blood flow were assessed by an intracoronary Doppler flow wire and blood was sampled from the coronary sinus for the measurement of C-reactive protein (CRP). The patients were then randomly divided into two groups; a nifedipine treatment group (long-acting nifedipine; nifedipine CR® 20mg/day) and a control group. After 120±7 days, coronary angiography was again performed for all the patients to evaluate the patency of the lesions and the procedures performed above were repeated on the same coronary artery.
Results: Baseline characteristics, prescribed medications, coronary risk factors and hemodynamic properties of the patients were the same in both groups. The incidence of coronary restenosis was 33.3% and 16.7% in the control and the nifedipine treatment groups, respectively (n.s.). Treatment with nifedipine markedly enhanced acetylcholine-induced increases in coronary blood flow (normalized by the response to ISDN; 1.67±0.42 to 3.56±0.64; $p<0.05$), while the response to acetylcholine did not change over the follow-up period in control patients. The vasomotor responses to ISDN were similar in the two groups, and no interval changes were noted in either group. Blood sampling revealed a decrease in serum levels of CRP in the nifedipine treatment group (0.35±0.09 to 0.07±0.01mg/dl; $p<0.05$), but not in the control group during the study interval.
Conclusion: These results suggest that treatment with nifedipine improves endothelial function in the coronary circulation and decreases inflammation of the coronary vascular wall. This may contribute to an improvement in myocardial perfusion as well as regression of coronary atherosclerosis.

P459 Velocity of coronary artery motion during the cardiac cycle: measurement by biplane coronary angiography

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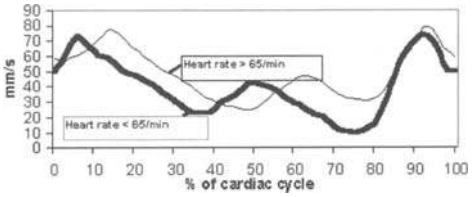
To minimize motion artifacts in coronary artery imaging by MRI, electron beam tomography and multislice spiral CT, image acquisition must be performed in the periods of slowest coronary artery motion. However, the exact patterns and velocity of 3-dimensional coronary artery motion are currently unknown.
Methods: In 30 patients with normal ventricular function (mean heart rate 68/min), biplane angiograms were obtained in orthogonal projections. After calibration, the spatial coordinates of predefined bifurcation points in the mid left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) were measured in every angiographic frame, 3-dimensional motion patters were reconstructed, and the motion velocity was calculated throughout the cardiac cycle.
Results: Mean coronary motion velocity was 42.6 mm/s (LAD: 24.7 mm/s, LCX: 38.6 mm/s, RCA: 64.4 mm/s). Highest velocity (mean: 72.4 mm/s). was observed at 92% of the cardiac cycle (atrial contraction). Two periods of slow motion were identified: during isovolumetric relaxation and in mid-diastole. For heart rates below 65/min (15 patients), slowest velocity was observed at 75% of the cardiac cycle, while for heart rates above 65/min (15 patients), slowest velocity was observed at 49% of the cardiac cycle (see graph).



Speed of coronary motion.

Conclusion: Coronary artery motion velocity displays substantial variation between the coronary vessels and during the cardiac cycle. To reduce motion artifacts, coronary imaging should be performed in mid-diastole for slow heart rates and in the period of isovolumetric relaxation for higher heart rates.

P460 Intravenous amiodarone administration increases markedly the coronary blood flow in intact swine heart

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Background: Amiodarone is a widely used antiarrhythmic agent with salutary effects on the clinical setting of heart failure and antianginal properties. The aim of our study was to evaluate the hemodynamics and coronary flow after intravenous infusion of amiodarone.
Methods: In eight opened chest pigs (weighting 65±6kgrs),two catheters (7F) were inserted in the aorta and the left ventricle and a third one (6F)was advanced in the right atrium. Transit time ultrasound flowmeter probes were placed around the left anterior descending coronary artery and the pneumonic artery trunk.
Intravenous amiodarone (5mg/kg body weight) was then administered over a period of five minutes. During the infusion of the drug, left ventricular peak systolic (LVSP) and end diastolic (LVEDP) pressures, mean (MAP) aortic pressure, right atrial pressure (RAP), heart rate (HR), pneumonic artery flow (PF) and coronary blood flow (CF) were recorded. Myocardial energy requirements [Tension Time Index (TTI)]were also evaluated.
Results: Amiodarone resulted in a decrease in TTI, HR, LVSP and MAP and an increase in CF, LVEDP and RAP (table)

	Baseline	1 min	5 min
CF (ml/mln)	70±21	128±53*	134±57*
PF (lt/min)	3.7±0.8	3.7±1.3	3.8±1.2
LVSP (mmHg)	121±26	109±23*	119±24
LVEDP (mmHg)	7±2	9±2**	10±3**
MAP (mmHg)	103±18	89±17*	87±24**
RAP (mmHg)	9±3	10±3*	11±4*
HR (bpm)	137±16	125±11*	125±17*
TTI (mmHg.s/min)	2778±571	2376±439**	2623±530*
		*p=0.01 vs Baseline	**p=0.05 vs Baseline

Conclusion: This experimental study demonstrates that intravenous amiodarone decreases heart rate and afterload and increases coronary blood flow, most likely by direct vasodilatation of the coronary arteries.

P461 Characterisation of fluid-dynamic properties of coronary artery stenoses by simultaneous intracoronary pressure and flow-velocity measurements

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Purpose: Examination of the fluid-dynamic properties of coronary artery stenoses in vivo by describing the changes in transstenotic pressure gradient - flow velocity relationships at rest and during maximal hyperemia.
Method: In 10 patients with different severity of coronary artery stenoses by QCA analysis intracoronary pressure and flow velocity measurements were performed simultaneously. Online parameter registration included the ECG recording, proximal coronary artery pressure (Pa), distal coronary artery pressure (Pd) and instantaneous peak velocity of coronary blood flow (V). Pd and V were registered with 0,014"-guide wires with integrated pressure and doppler transformers. Continous data acquisition was performed with a sampling rate of 200 Hz at rest and during maximal hyperemia induced with i.v. adenosin (140μg/kg/min). Prior to all measurements 0.5 mg of nitroglycerin were administered i.c. in order to keep the effects of epicardial artery vasodilation on stenosis geometry at a minimum. Data processing was done with MATLAB version 6.1.
Results: All recordings of the measurements in 10 subjects were performed successfully. The data was evaluated after the elemination of the accelerative phase of early diastole and the decelerative phase of systole. Using these data the passive diastolic pressure gradient - flow velocity characteristics were described by quadratic curvilinears. The slopes of these separate curves changed in correlation to apparent differences in angiographic stenosis severity.
Conclusions: At present the analysis of the passive diastolic relationship between pressure gradient and flow velocity at rest and during maximal hyperemia probably yields the most comprehensive description of the fluid-dynamic properties of a coronary artery stenosis. We show that in vivo measurements in humans can be performed reliably. With respect to our preliminary data the pressure gradient - velocity curves may allow a classification into categories of mild, moderate, and severe stenoses based on fluid-dynamic characteristics of a stenosis. Weather this method will give superior information to the use of intracoronary pressure or flow velocity measurements with determination of the myocardial fractional flow reserve (FFRmyo) or the coronary flow velocity reserve (CFVR) alone is still unclear. Further investigations are required to determine the potential value in interventional clinical cardiology.

P462 Evaluation of coronary flow reserve before and after left anterior descending artery stent implantation: a transoesophageal echocardiography study

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Coronary angioplasty and stent implantation is widely used procedure for the treatment of coronary artery disease. Coronary flow reserve (CFR) is considered a precise indicator of the functional significance of coronary stenosis. Transesophageal echocardiography (TEE) is becoming a useful tool for evaluation of CFR in the proximal left anterior descending artery (LAD), and can be used as a non-invasive index of restenosis.
Objectives: To evaluate CFR by TEE before and 48 hours (h) after LAD stenting; to determine the predictors of post-procedural CFR impairment; and to evaluate the diagnostic accuracy of transesophageal Doppler CFR measurements for prediction of restenosis.
Methods: To determine normal flow velocities, we studied a control group of 20 healthy volunteers, mean age 49,1±10,7 years, 7 males. The stenosis group comprised 51 patients (pts) (mean age 59,5±10,4 years, 29 males) with LAD stenosis (> 50%). Successful LAD stenting were performed in all stenosis group pts. Quantitative coronary angiography was done before and after the procedure. CFR was measured by TEE, with spectral Doppler recordings of flow in baseline conditions and during a 4 min infusion of adenosine (140 μg/Kg/min). After 6 months, CFR by TEE and selective angiography was repeated for detection of restenosis.
Results: Feasibility of CFR measurements was 91%, and intraobserver variability was 2,8±1,4%. CFR was significantly lower in stenosis group (1,89±0,66) than in control group (3,82±1,15); $p < 0,001$. Stenosis group presented a statistically significant increase of CFR 48 h after stenting, from 1,89±0,66 to 2,58±0,76 ($p < 0,001$). However, 55% of pts remained with impaired CFR (< 2,5). Multivariate logistic regression analysis showed that multiarterial lesions, age and lesion extension were the determinants of flow impairment after successful stenting. 41 pts of stenosis group completed 6 months follow-up, and angiographic restenosis were detected in 39% of them. CFR for pts with restenosis (1,91±0,54) was lower than that for pts with no restenosis (2,37±0,71), $p < 0,05$. A reduced CFR had good sensibility (94%), but poor specificity (48%) for the diagnosis of restenosis.
Conclusions: TEE is a feasible and safe method for evaluation of CFR, and allows non-invasive identification of pts with lesion > 50% in LAD. It can be used for serial assessment of CFR before and after stent implantation. However, TEE presents limitations for the diagnosis of restenosis, probably due to multifactorial process that alters CFR in pts with established coronary artery disease.

P463 Improved myocardial blush grade post primary angioplasty is associated with reduced peak troponin I elevation

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Background: Improved myocardial blush post thrombolytic therapy for acute myocardial infarction (AMI) is associated with improved clinical outcomes however the mechanism for this has not been fully established. We sought to address whether reduced myocardial injury as manifested by reduced peak post procedural troponin I was the mechanism of this improvement in a cohort of AMI patients treated with primary angioplasty.
Methods: The coronary angiogram and primary PTCA films of 93 consecutive patients (68 males, age 60.8 ± 14.1 years), presenting with acute myocardial infarction within 6 hours after symptom onset and treated with primary angioplasty, were analysed. TIMI flow and myocardial blush grade (MBG) were evaluated in the culprit artery and subserving myocardial territory respectively, both at baseline and following PTCA and stenting. MBG was graded 0: no blush; 1: minimal blush; 2: moderate blush; 3: normal blush. Peak post procedural troponin I, mortality and target lesion vessel revascularisation rates were recorded in each case.
Results: Peak post procedural troponin I elevation was increased in patients who had poor myocardial perfusion (MBG 0 or 1, n=41) following angioplasty and stenting compared to those with good myocardial perfusion (MBG 2 or 3, n=52) (44.3 ± 8.3 v 17.6 ± 3.2 μg/L, mean ± SEM $p < 0.01$). There was no difference between the two groups in baseline characteristics including age, sex and culprit lesion. A trend to increased mortality in patients with poor post procedural myocardial perfusion was present (7 v 3, p NS). Target lesion revascularisation rates were lower in those with poor myocardial perfusion (4 v 6, p NS).
Conclusion: Improved myocardial blush grade following primary angioplasty is associated with reduced myocardial injury as assessed by troponin I elevation and better clinical outcome. The mechanism is likely to be enhanced microvascular perfusion. Routine assessment of myocardial blush grade following angioplasty and stent deployment is a useful tool for predicting outcomes in AMI patients treated with primary angioplasty.

P464 Influence of side branch on Coronary Flow Reserve (CFR). Measurement by guide wire based thermodilution in the experimental models

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Background: Fractional flow reserve (FFR) and coronary flow reserve (CFR) are physiological indices of coronary artery stenosis severity. FFR and CFR could only be obtained by 2 separate guidewires previously. Recently, a combined 0.014 pressure/temperature sensor-mounted guide wire has been developed to measure FFR and CFR by thermodilution (CFR-thermo) simultaneously. We aimed to assess the accuracy of CFR-thermo compared with CFR obtained by flow rate (CFR-flow) in the experimental models. Methods: Using experimental models made by the straight-rigid tube (4mm diameter) without stenosis and side branch filled with 36°C water, CFR-thermo and CFR-flow were measured under the different conditions of the sensor position and the injected water temperature (0°C to 40°C). Side branch (2mm diameter) was placed on 4, 6, 8 and 10cm from the injected site just proximal to the stenosis. The degree of stenosis ranged from 0 to 75% (0, 25, 50, 75%). CFR-thermo and CFR-flow were calculated by the inverse ratio of the mean transit time and the flow ratio during high flow to low flow rate, respectively. Results: Under the condition without side branch, there was good correlation between CFR-thermo and CFR-flow when a temperature of injected water was under 32°C and the termo-semsor was not placed within 4 cm from the injection site. In cases with side branch and the stenosis, CFR-thermo were underestimated compared with CFR-flow although there was good correlation between CFR-thermo and CFR-flow. The more proximally placed the side branch to injected site, the more CFR-thermo was underestimated compared with CFR-flow. Conclusions: Temperature of injected water, and the position of sensor, a side branch and stenotic lesion may influence on CFR-thermo. These should be taken into account when CFR would be measured by thermodilution method.

P465 Subendocardial and subepicardial blood flow in normals and patients with coronary artery disease

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Introduction: Clinical studies in humans and experimental work in animals suggest that in coronary artery disease (CAD) the subendocardium (ENDO) is more susceptible to ischaemia than the subepicardium (EPI). So far, technical limitations have prevented the confirmation of this finding in humans. We measured absolute ENDO and EPI blood flow (MBF) in normal subjects and in patients with CAD using a high sensitivity PET scanner (EXACT3D).
Methods: We studied seven normal volunteers (age 48±2) and ten patients (61±8, $p<0.05$) with stenoses of >70% in two or more coronary arteries. All subjects underwent PET scanning, using oxygen-15 water, at rest and at a maximal tolerated dose of dobutamine. At analysis the LV wall was divided into septal, anterior, lateral, and inferior walls. Each wall was further subdivided into apical and basal segments and then equal ENDO and EPI halves. The segments perfused by each stenosed coronary artery were identified using conventional recommendations. The oxygen-15 water kinetic was fitted to a model corrected for spillover from both ventricular cavities and for partial volume. MBF is presented as ml/min/g of myocardium.
Results: Resting ENDO and EPI MBF (mean±SEM) were 0.92±0.05 and 0.74±0.05 ml/min/g in normals and 0.98±0.06 and 0.77±0.05 ml/min/g in patients (ENDO vs EPI $p<0.0001$ for each group). The rate pressure product in normals increased by 262±39% at a maximum dobutamine dose of 36±5 μg/kg/min and by 210±48% (p=0.03 vs normals) at 32±4 μg/kg/min (p=ns) of dobutamine in patients. In normals, dobutamine MBF increased in 98% of ENDO segments (flow fell in one segment by 0.01 ml/min/g) to 2.40±0.12 ml/min/g and in all EPI segments to 2.30±0.13 ml/min/g. In patients, ENDO dobutamine MBF was 1.3±0.10 ml/min/g and EPI 1.3±0.12 ml/min/g. All patients experienced chest pain and developed ischaemic ECG changes at peak stress and, at this time, MBF fell compared to baseline in 36% of ischaemic ENDO segments and in 25% of EPI segments. ENDO coronary vasodilator reserve (CVR=stress MBF/rest MBF) was 3.0±0.2 in controls and 1.4±0.1 in patients (normals vs CAD $p<0.0001$) and EPI CVR was 3.5±0.2 and 1.8±0.2 ($p<0.0001$) respectively.
Conclusion: Despite an increase in workload, stress MBF falls in a significant proportion of both ENDO and EPI segments perfused by a stenosed coronary artery. The mismatch between demand and supply is greater in ENDO than EPI segments and this may contribute to the greater susceptibility of this layer to myocardial ischaemia.

P466 Myocardial fractional flow reserve and coronary flow ratio in children with Kawasaki disease

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We investigated the detection of silent myocardial ischemia and the effectiveness after PTCA and CABG using myocardial fractional flow reserve (FFRmyo) and coronary flow ratio(CFR) in children with Kawasaki disease (KD). 136 patients (1y-15y) with isolated lesion in one major epicardial coronary artery, normal left ventricular function were divided into three groups; myocardial ischemia (IS) group (n=34), non-ischemia with coronary aneurysm and stenosis (n-IS) group (n=38), and coronary dilation without coronary stenosis (N) group (n= 64) by rest and exercised myocardial scintigraphy and CAG. Pressures were measured at orifice of coronary artery and graft arteries, distal portion of coronary arterial stenotic lesions, anastomosis of arteries, dilated portions by PTCA, and right atrium at the same time. FFRmyo is defined as the ratio of maximal achievable flow in myocardium subtended by a stenosed coronary artery to the maximal achievable myocardial flow induced by papaverine (0.2mg/kg in LCA, 0.15mg/kg in RCA), and FFRmyo can be calculated as next formula; FFRmyo =(Pc-Pv)/Pao-Pv), Pc: mean coronary pressure at distal of stenotic lesions, Pao: mean aortic pressure, Pv: mean right atrial pressure. Average peak velocities were measured at distal portion of stenotic lesions in both rest and papaverine stress(same dose in FFRmyo). CFR was calculated as a ratio of APV before and after papaverine stress at the same positions of FFRmyo. Results: Criteria for detection of myocardial ischemia were defined the mean ± 2SDs for FFRmyo and CFR in N group (Criteria for detection of myocardial ischemia: FFRmyo < 0.75, CFR< 2.0). FFRmyo and CFR were significantly low in IS group (0.64±0.3, 1.1±0.2) as compared to those in n-IS group (0.91±0.6, 2.9±0.5) and N group (0.90±0.7, 3.1±0.5). Sensitivity and specificity for detection of myocardial ischemia were very high by FFRmyo (100%,100%) and CFR (93.7%, 96.8%). Moreover, FFRmyo and CFR pre-PTCA (n=7: 0.62±0.5, 1.1±0.4) and pre-CABG (n=8: 0.60±0.6, 1.2±0.3) were abnormal. But, after PTCA and CABG these values turned to normal same as findings of CAG and clinical.
Conclusions: Criteria of FFRmyo and CFR for detection of myocardial ischemia are the same values in adult. FFRmyo and CFR can be helpful to estimate myocardial ischemia and to evaluate the effectiveness of PTCA and CABG in children with KD.

P467 Change in TIMI frame count correlates with the change in coronary flow parameters

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Background: TIMI frame count (TFC) was introduced as a quantitative and continuous method for defining the coronary blood flow. The data regarding the TFC as compared to Doppler flow wire parameters are limited. We sought to determine the correlation of percent change in TFC with the change in coronary flow parameters in response to acetylcholine (Ach)and nitroglycerin.
Methods: Fifty seven consecutive patients (18 males) without obstructive coronary artery disease underwent coronary physiologic study in the Mayo Clinic were included in the study. Coronary flow parameters were assessed using a Doppler guidewire at baseline, after 0.182, 1.82 and 18.2 microgram/mL concentrations of Ach infusion and after 200 microgram nitroglycerin in left anterior descending arteries. Coronary artery diameters were assessed by quantitative coronary angiography. In each patient a distal landmark was defined in left anterior descending artery and TFCs (number of frames required for the contrast to travel from the ostium to distal landmark) were calculated at baseline and after each Ach infusion and nitroglycerin injection. The percent change in TFC from baseline was compared to the percent changes in averaged peak velocity (APV), coronary artery diameter (CAD), and coronary blood flow (CBF) after each Ach and nitroglycerin administration. Also, a new TFC index (TFCI) was defined as the vessel area divided by TFC and percent change in the TFCI from baseline was then calculated and compared with the change in coronary blood flow.
Results: The correlations of the variables stated above at the end of 208 measurements in 57 patients are shown in the table:

	Spearman R	p
d TFC vs. d APV	- 0.66	< 0.001
d TFC vs. d CAD	0.30	< 0.001
d TFC vs. d CBF	-0.40	< 0.001
d TFCI vs. d CBF	0.77	< 0.001

d: percent change; vs.:versus

Conclusion: Percent change in TFC correlated significantly with the percent change in APV. There is a good correlation between the change in TFCI and change in coronary blood flow. TFCI can reflect the changes in coronary blood flow and can be used as a simple and reliable method of assessment of coronary blood flow.

P468 Coronary flow velocity reserve does not correlate with TIMI frame count in patients undergoing non-emergent percutaneous coronary intervention

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Corrected TIMI frame count (CTFC), a quantitative yet simple angiographic measure of blood flow, is a predictive marker of outcome in the setting of reperfused myocardial infarction. However, much less is known about the physiological relevance of CTFC in patients undergoing non-emergent percutaneous coronary intervention (PCI). In elective procedures, doppler derived measurements of coronary flow velocity reserve (CFVR) have proven useful in predicting outcomes of PCI, but expense limits general use. Since both CFVR and CTFC are a measure of coronary blood flow, we hypothesized that the two measures would be related. The objective of this study was to compare the CTFC with CFVR in patients undergoing non-emergent PCI. We studied 62 patients with TIMI 3 flow who underwent successful non-emergent PCI as part of a randomized multi-centre study of coronary stenting and optimal balloon angioplasty (Doppler Endpoint Stenting International Investigation). All patients had doppler evaluation of CVR, CTFC and QCA pre and post intervention.
PCI increased minimal lumen diameter (MLD) from 0.94 ± 0.32 to 2.78 ± 0.54 mm (% stenosis: 69 ± 10 to15 ±11%). The CTFC decreased from 27 ± 13 to 18 ± 8 and CVR increased from 1.5 ±0.4 to 2.6 ± 0.7 (both $p<0.0001$). Although the pre PCI CTFC and the CFVR were closely related to MLD ($p<0.0001$) there was no relationship between CTFC and CFVR pre intervention (p=0.12). Following PCI, there was no correlation between CTFC and CFVR or other doppler parameters. The post intervention CTFC was closely related to pre CTFC (p=0.003). Interestingly, post-PCI, the CTFC/MLD ratio correlated with CFVR ($p<0.05$).
Conclusion: There was no correlation between CTFC and doppler derived parameters in patients undergoing non-emergent coronary intervention but there was a relationship between CVR and the CTFC/MLD ratio. The utility of CTFC in predicting outcomes in this setting requires further evaluation.

P469 Relation between postprocedural TIMI frame count and functional recovery after revascularization of viable myocardium

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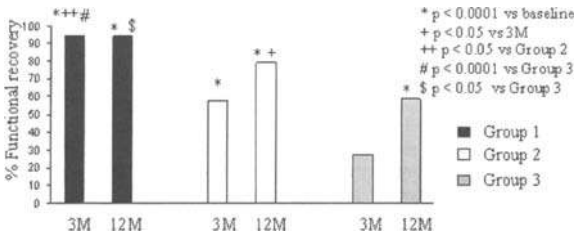
Introduction: It has been reported that postprocedural angiographic flow, evaluated by the TIMI frame count (cTFC) method, may affect regional functional recovery of patients undergoing primary PTCA. No extensive data have been so far published about the relationship between postprocedural cTFC and long-term functional recovery of viable myocardium in patients with chronic coronary artery disease undergoing coronary angioplasty (PTCA).
Methods and Materials: From a consecutive series of patients undergoing evaluation of myocardial viabiltiy at our Institute, we selected patients that underwent singlevessel revascularization by PTCA. Thus 21 patients (59±12 ys, 3 females) represented the population of the current study. They underwent rest-redistribution 201Tl SPECT and echocardiogram at rest before revascularization, at three months (3M) and 1 year (12M) after revascularization. Patients were devided in three groups according to postprocedural cTFC: Group 1 (< 13 frames; 6 pts), Group 2 (13-23 frames; 10 pts) and Group 3 (> 23 frames; 5 pts).
Results: See Figure.



Conclusions: Our study demonstrated that the timing of functional recovery after revascularization of viable myocardium is significantly affected by post-procedural angiographic coronary flow. Thus for a correct assessment of viability, echocardiographic follow-up should be prolonged at least till one year after revascularization.

P470 Risk stratification using different cut-off values of fractional and coronary flow reserve after deferral of PTCA of intermediate lesions

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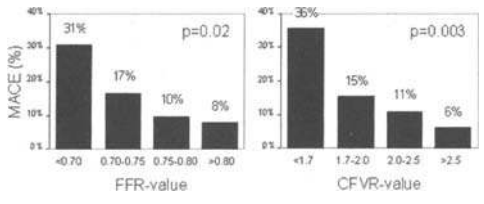
Purpose: To evaluate deferral of PTCA in intermediate lesions (40-70% diameter stenosis using different thresholds for fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR).
Methods: PTCA was deferred in 130 patients, including 141 coronary lesions (mean diameter stenosis of 55%)based upon normal myocardial perfusion stress testing and/or discordant results between CFVR and FFR. Both intracoronary pressure and flow velocity were obtained during baseline and maximum hyperemia (by 15-20 mcg adenosine IC). FFR was defined as the ratio of mean distal pressure to mean aortic pressure during maximum hyperemia and CFVR was defined as the ratio of hyperemic to baseline flow velocity. Patients were followed for one year to document major adverse cardiac events (MACE: death, myocardial infarction (MI), CABG, PTCA) related to the intermediate lesion. Patients were divided into quartiles determined by the distribution of MACE and the established cut-off values used for FFR (0.75) and CFVR (2.0).
Results: A total of 16 (11%, 5x MI, 2x CABG, 9x PTCA) events occurred during follow up. There was a significant positive trend between the occurrence of MACE and the used cut-off values of FFR (p=0.017, Cochrane Armatege test) and CFVR (p=0.0025), see figure below.



Conclusion: Differentiation of threshold values of FFR and CFVR allows risk stratification in patients following deferral of PTCA of intermediate coronary lesions.

P471 Feasibility of assessment of coronary fractional flow reserve during ambulatory coronary angiography

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Purpose: To assess the feasibility of coronary fractional flow reserve (FFR) assessment in outpatients through diagnostic 4 or 5 French catheters.
Methods: Over 1 year, FFR was determined using pressure flow wire (Endosonics) in consecutive patients in case of intermediate angiographic stenosis (40 to 60% diameter stenosis (DS) by quantitative coronary analysis) and lack of demonstrated ischemia. FFR was measured using a 4 or 5F diagnostic catheter or through a 7F guiding catheter, after injection of 0.2mg adenosine intracoronary. All patients received 2500IU heparin before FFR assessment. When no additional procedure was needed, heparin was neutralised with 2.5 ml protamine and the sheath removed immediately. When diagnostic catheter was used, strict bed rest was required for only 3 hours and patients were allowed to discharge on the same day.
Results: FFR was measured in 145 patients (156 lesions) using a 7F guiding catheter (n=54) or a diagnostic catheter (n=91): 5F(n=46) and a 4F(n=45). Results of the quantitative coronary analysis and of FFR are displayed in the table. Feasibility of pressure guide wire placement was similar through diagnostic or guiding catheter and there was no difference in pressure curve quality. 31(20%) lesions were submitted to immediate angioplasty, 5(3%) delayed angioplasty, 9(6%) delayed surgery. All 107(74%) patients not requiring additional procedure were candidates for early discharge. When a 4 or 5F catheter was used, ambulation was allowed after 3 hours and half of these patients were discharged at the same day. No angiography or FFR measurement-related complication occurred.

	7F	5F	4F
N of pts (lesions)	54 (55)	46 (51)	45 (50)
DS (mm)	0.53±0.08	0.43±0.06	0.45±0.12
FFR	0.86±0.06	0.91±0.08	0.87±0.21
Protamine post FFR	7 (16%)	19 (40%)	25 (56%)
Outpatients	1/54 (2%)	3/46 (6%)	20/45 (44%)

Conclusion: FFR measurement through 4 or 5F diagnostic catheter is feasible and safe and therefore is possible during outpatient coronary angiography.

P472 Intravenous adenosine during coronary flow reserve assessment: is 90-second infusion sufficient for maximal coronary vasodilatation?

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Background: The timing of i.v. adenosine infusion during coronary flow reserve (CFR) evaluation varies among different studies. Recent studies have used a 90-second i.v. adenosine for CFR assessment. We sought to test if CFR measured within 90 seconds after adenosine infusion can induce maximal coronary vasodilatation, when compared with standard 5-minute protocol.
Methods: Two-hundred twelve patients suspected of coronary artery disease were studied. Flow velocity in the distal left anterior descending coronary artery (LAD) was noninvasively evaluated at rest and during i.v. adenosine (140μg/kg/min in 5 minutes) by transthoracic Levovist enhanced harmonic Doppler echocardiography. The maximum hyperemic peak flow velocity averaged over 3 cardiac cycles within 90 seconds and 5 minutes were calculated, and CFR values within 90 seconds (CFR-90s) and 5 minutes (CFR-5m) were determined respectively.
Results: Three patients (1.4%) could not achieve flow signal in the LAD and 12 (5.6%) could not finish 5-minute adenosine infusion because of chest pain (5), ECG ST depression>1mm (4) or hypotension (3). CFR-90s and CFR-5m were successfully acquired in 197 patients (92.9%). In 186 patients (94.4%) the highest hyperemic response during 5-minute adenosine infusion was occurred within the first 90 seconds, i.e., CFR-5m equals to CFR-90s; whereas in 11 (5.6%) CFR-5m was significantly higher than CFR-90s (2.46 ± 0.70 vs. 2.12±0.57, p<0.01). Among these patients, 7 (63.6%) had a pattern of fluctuating flow during adenosine infusion. Heart rate and blood pressure were not significantly different within 90 seconds and 5 minutes.
Conclusions: Although in majority of patients the maximum hyperemic response appeared within the first 90 seconds after adenosine infusion, in approximately 5% of patients CFR was significantly underestimated when calculated within 90-second infusion. Therefore, when no severe side effects are present, 5-minute adenosine infusion should be preferred for CFR assessment.

P473 Coronary flow reserve immediately after reperfusion predicts infarct size in patients with acute myocardial infarction without diabetes mellitus

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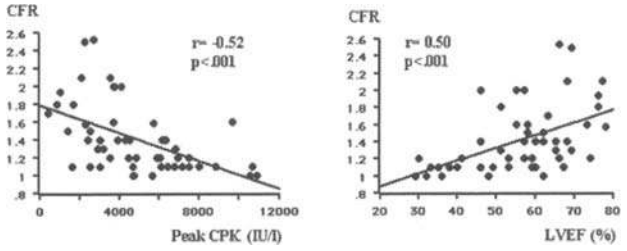
Background: The aim of this study was to examine the clinical value of coronary flow reserve (CFR) measured immediately after reperfusion in predicting infarct size.
Methods: We studied 73 patients (pts) with a first anterior wall myocardial infarction who underwent primary coronary angioplasty successfully. By using a Doppler guidewire, CFR was assessed immediately after primary coronary angioplasty. The patients were divided into two groups: diabetic group (n=19) and non-diabetic group (n=54). We used peak CPK and left ventricular ejection fraction (LVEF) at 2-3 weeks follow-up as markers of infarct size.
Results: By regression analysis, CFR significantly correlated to peak CPK and LVEF in non-diabetic pts (r= -0.52 and r=0.50, respectively, p<.001), whereas there was no correlation in diabetic pts (r= -0.36 and r=0.06, respectively, p=NS).



CFR and infarct size in non-diabetic pts.

Conclusion: CFR measured immediately after reperfusion can predict infarct size in pts with non-diabetic anterior AMI.

P474 Coronary artery fistulas in adults: blood flow pattern and effect on myocardial perfusion

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Background: Congenital fistulae are the most common coronary arterial malformation and are being recognized with increased frequency with the widespread use of selective arteriography.
In this study we assess for first time the effect of these malformations on coronary circulation and myocardial perfusion in adults.
Methods: Of the 830 patients who underwent diagnostic catheterization in our laboratory, 11 (1.3%) had coronary artery fistulas. All of them performed exercise stress myocardial perfusion scintigraphy. In 6 patients, whose fistulas had diameters greater than 2mm, we placed a 0.014" Doppler guidewire a) at the vessel where the fistulae was originated from and b) into the fistula itself to estimate coronary blood flow. Volumetric flow was calculated as the product of flow velocity integral (systolic, diastolic or total by the estimation of respective flows), heart rate and cross-sectional area (CSA) of the vessel at the tip of the wire.
Results: Seven fistulas originated from the right, 3 from the circumflex and 1 from the left anterior descending coronary artery. None of these vessels had coronary artery disease. The mean ratio of pulmonary to systemic flow was 1.12±1.55 and both right and left heart chambers pressures were within normal range. No one of the patients had a thallium myocardial scintigraphy with evidence of a perfusion defect at the region supplied by the vessel where fistulae originated from. In all cases, the flow through the fistula occurred mainly during systole [diastolic to systolic flow ratio (DSFR): 0.3±0.2] while the flow in the vessel where the fistulae originated from was mainly during the diastolic phase of the cardiac cycle (DSFR: 3.2±0.5).
Conclusions: Coronary artery fistulas do not seem to impair myocardial perfusion in adults, confirming the view of their good prognosis. The main reason seems to be that the blood flow through the fistula occurred mainly during the systolic phase of the cardiac cycle, minimally affecting coronary perfusion, which takes place during diastole.

P475 X-ray exposure during coronary angiography: importance of lowering RX emission protocols

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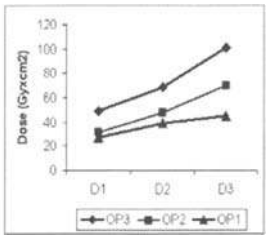
Radiation dose received by the patient during invasive cardiology procedures is multifactorial, depending on the duration of procedures, body surface area and application of X-Ray rules (frames/sec, fluoroscopy dose, cine dose, collimation, intensifier-patient distance, field size), and is cumulative.

In order to evaluate the influence of different X-Ray protocols on patient radiation, we analyzed 2488 consecutive patients (mean age: 65.8 years, 75% males) for whom a diagnostic coronary angiogram was performed by 3 high-volume operators (OP1,OP2,OP3). For each patient, body surface area (BSA), total X-Ray dose (analyzed by Diamentor®), radiation time, type of fluoro (low, medium or high), type of cine dose (A,B,C,D from the lowest to the highest), cine frame rate (8 or 12.5 frames/sec), were collected.X-Ray protocols were significantly different between the 3 operators, leading to significant differences in radiation doses.In order to avoid the influence of radiation time, patients were equally divided into 3 equal groups according to the radiation time (D1: <171 sec; D2: 172-290 sec, D3 >290 sec). BSA was not different between the 3 groups and between operators, but a significant difference in total X-Ray doses was observed between operators for each duration; the shorter procedures performed by OP3 were as irradiating as the longer procedures performed by OP1.

	OP1	OP2	OP3
% 8 fr/sec	64.0%	31.6%	24.6%
% low fluo	91.5%	39.8%	62.6%
% cine A/B	41.9%	33.3%	38.6%
Dose (Gyxcm2)	33+-24	64+-40	64+-41



Protocols and dose.

Conclusion: lowering frame rate and lowering X-Ray emission can dramatically decrease X-Ray exposure for the patient, independently of body mass area and of duration of X-Ray exposure. As this strategy has no consequence for the accuracy of the diagnosis, operators should be encouraged to change their protocol in order to reduce radiation as low as possible, especially in longer procedures.

P476 Appropriatness of invasive coronary investigation: a prospective single centre analysis on 875 consecutive patients

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Evaluations of the appropriatness of medical care are important to monitor the quality of care and to contain costs and enhance safety by reducing inappropriate care. Investigators at RAND have developed a specific method for clinical experts to rate the appropriatness of medical care. It consists of a panel of physicians who, following medical guidelines in the different fields to evaluate, use a scoring system to classify the procedures into three categories: appropriate, uncertain and inappropriate. Following the RAND appropriatness method, criteria were developed for the appropriate use of coronary angiograms and coronary revascularisation procedures (PCI=percutaneous coronary intervention, CABG = coronary artery bypass graft)in Switzerland. Based on the Swiss RAND criteria a system prototype has been implemented on the basis of Internet/database technology. The SOS (second opinion system) allows to compare one's own results with an Internet panel. By connecting our computerized database with the Swiss SOS we were able to evaluate in a prospective manner the appropriatness of our diagnostic and therapeutic procedures. We report the first 6 months analysis performed at our institution from January to June 2001 over 875 consecutive angiograms and 442 revascularisation interventions (292 PCI and 150 CABG). The results are summarized in the table and divided, following the RAND recommendations into the three categories: appropriate, uncertain and inappropriate

	Appropriatness		
	Angiograms N (%)	PCI N (%)	CABG N (%)
Appropriate	727 (85)	281 (96)	149 (98)
Uncertain	107 (12)	11 (4)	1 (2)
Inappropriate	41 (5)	0	0
Total	875 (100)	292 (100)	150 (100)

Conclusions: 1. Internet decision-making tools for indications and therapeutical decisions may be a valuable tools in medical quality management and represents an interesting method to evaluate the on line appropriatness for invasive procedures.
2. Our analysis contains several intrinsic and procedurale bias and the results, although very convincing, must be interpreted very carefully

P477 Radiation dose reduction with digital flat panel cardiac x-ray imaging

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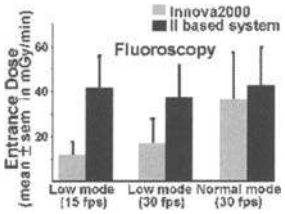
Background: The growing use of coronary angiography and percutaneous interventions highlights the importance of minimizing radiation exposure to patients undergoing cardiovascular x-ray angiographic procedures. Excess radiation doses may produce significant acute and late effects, ranging from cutaneous manifestations to carcinogenesis. Fully digital cardiovascular x-ray imaging systems have recently been developed using flat panel detector technology (DFP); the theoretical reduction in dose afforded by this technology has not been largely documented in comparison with a traditional image intensifier (II) system.
Methods: Entrance dose measurements were made using a DFP cardiac system (Innova 2000, GE) and a non-GE II-based system. For each system, the dose was measured using an ionization chamber for 10, 15, 20, 25 and 30 cm of Plexiglas with the center of the Plexiglas phantom maintained at the isocenter of the image system gantry. Dose measurements were made for each system in all dose modes available for both fluoroscopy and record modes, for all frame rates available, and for each magnification mode. Entrance dose measurements are corrected to the entrance surface of the phantom and include backscatter.
Results: On fluoroscopy mode, the DFP system compared favorably to the II based system for each dose settings, i.e 15 and 30 frames per second (fps), in "Low" and "Normal" modes (table 1). Similar results were obtained on record mode at both 15 and 30 fps. On average, the DFP system resulted in significantly lower entrance exposure dose compared with the II system.



Conclusion: This study demonstrates that the DFP based cardiac system has the potential to significantly decrease radiation exposure during fluoroscopy and cine angiography.

P478 Is gridless angiography a dose-saving alternative on a Digital Flat Panel cardiac system?

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Background: The anti-scatter grid is widely used in general X-ray imaging techniques. Its primary purpose is to reduce secondary radiation and improve contrast in the image. However, the use of a grid results in much more radiation being delivered to the patient. This study seeks to evaluate whether the removal of the grid on the newly introduced Digital Flat Panel (DFP) system could be an alternative for a daily routine practice.
Methods: Thirty three randomly selected patients underwent an angioplasty procedure with a fixed grid whilst 35 patients underwent an angioplasty procedure after the grid had been removed from the system and replaced by the air-gap technique. All procedures were performed on a DFP cardiac system (Innova 2000, GE). For each patient sex, BMI, fluoroscopy and record times as well as X-ray dose (expressed as Dose Area Product: DAP) were monitored. Three experienced cardiologists were asked to rate the image quality (IQ) on an 11-point scale (1=Excellent; 6=Satisfactory; 11=Poor IQ).
Results: The group "With Grid" was comparable to the one "Without Grid" in terms of sex, BMI, fluoroscopy and record times. However, a significantly lower dose was delivered to patients undergoing procedures without a grid in comparison to those procedures with a grid (table). The relative dose saving was 31.6% after grid removal (on log-transformed data). Even though the IQ was rated as slightly better for the "With Grid" group (p=0.04), images without the grid were rated as significantly better than a satisfactory IQ (p=0.01).

	"With Grid" (n=33) Mean±SD	"Without Grid" (n=35) Mean±SD	p-value	
Sex (M/F)	27/6	26/9	0.5	NS
BMI (kg/m^2)	27.7±3.2	26.7±3.7	0.3	NS
Fluoroscopy time (min)	7.9±5.2	7.3±6.0	0.3	NS
Record time (sec)	45.4±26.9	38.5±20.2	0.3	NS
DAP (cGy cm^2)	5177.6±3223	3735.5±2848	0.01	S
Image quality	4.11±0.9	5.12±1.1	0.04	S

Conclusion: This study demonstrates that the removal of the grid on a DFP cardiac system has the potential to significantly decrease the radiation dose to the patient with an image quality that is more than satisfactory.

P479 Should follow-up angiography be routine in asymptomatic patients after stenting of unprotected left main coronary stenosis?

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Background: Selected patients with unprotected left main coronary artery (ULMCA) stenosis can safely undergo stenting. Clinical restenosis after stenting of ULMCA occurs in 8-15%. Earlier studies predominantly utilizing non-stent devices revealed approximately 10% incidence of death at follow-up, perhaps due to rapidly progressive restenosis. This led to the recommendation of routine angiography at 3-4 months after ULMCA intervention. However, its practical utility after ULMCA stenting is controversial. We present complete one-year follow-up of first 120 consecutive high-risk cases of ULMCA stenting deemed unsuitable for CABG.
Methods: Baseline: mean age 82±6 yrs, female 42%, mean LVEF 31±14%, GP inhibitors in 76%, and elective IABP in 34%. Stenosis location: ostium in 25%, body/distal in 60%, and bifurcation in 15%. All patients underwent stenting, 89% after rotablation.
Results: Procedure was successful in all patients without any major in-hospital complications. Vascular complications occurred in 3%. Mean reference vessel diameter was 3.81±0.81 mm, MLD pre-procedure 1.12±0.36 mm and post-procedure 3.67±0.52 mm. CK-MB elevation occurred in 21%, with >5x normal in 4%. All patients were discharged alive at a mean duration of 6±5 days. At one-year follow-up there have been 16 deaths: 8 cardiac (4 CHF, 2 MI, 1 arrhythmia, 1 stent thrombosis), 8 non-cardiac (3 CVA, 3 pneumonia, 1 hyperkaliemia, 1 neoplasm). A total of 14 patients (12%) required repeat intervention for recurrence of angina, heart failure, or positive non-invasive testing. On multivariate analysis, bifurcation lesion intervention (OR 4.2; 95% CI 2.2-6.8) and diabetes (OR 2.4; 95% CI 1.8-3.2) were independent predictors of restenosis. No patients underwent CABG or had sudden death at follow-up. Protocol mandated angiography was done in 42 asymptomatic patients and none had >70% stenosis of LMCA.
Conclusion: Present prospective careful observation suggests that ULMCA in-stent restenosis always manifests clinically. Extremely low incidence of sudden death at follow-up may obviate the need of routine follow-up angiography in these high-risk ULMCA patients. Whether this observation can be generalized to all ULMCA stent patients needs to be determined.

P480 Is there collateral flow in normal coronary arteries?

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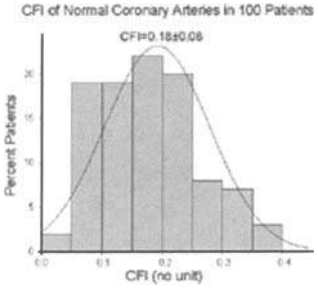
Background: Pathologic studies in the past hundred years have described the human coronary circulation to be with or without anastomoses between different vascular regions. In time of first experiences in therapeutic arteriogenesis in the human coronary circulation, it is unknown if there is collateral flow via pre-existing anastomoses in vivo among patients (pts) with angiographically normal coronary arteries.
Methods: In 100 pts collateral flow index (CFI, no unit) was measured in coronary arteries without any stenoses. CFI was determined by simultaneous measurement of mean aortic pressure, central venous pressure and coronary wedge pressure via sensor-tipped guidewire at the end of 1-minute occlusion. Patients were subdivided into two groups according to angiographically determined absence (51 pts) or presence (49 pts) of stenotic lesions in vessels other than that undergoing collateral measurement.
Results: CFI in 100 pts (61 ± 10 years, men/women 69/31) averaged 0.18±0.08 in a normal gaussian pattern, figure. In the two groups differences in CFI (0.19 ± 0.10 vs. 0.17 ±0.07), absence of angina (13/51 vs. 13/49) and pathological intracoronary ECG-changes during measurement (10/51 vs. 7/49) were not significant (ns). CFI in the recipient vessels LAD/LCX/RCA was 0.17 ± 0.08/0.19 ± 0.09/0.17 ± 0.08 (ns).



Conclusions: These findings suggest, that there is flow in preexisting collaterals even in pts with angiographical entirely normal coronary arteries. This is in contradiction to common knowledge indicating that coronary anastomoses develop de novo in a myocardial area jeopardized by ischemia.

P481 Collateral pathway anatomy and collateral function: a new angiographic grading validated by invasive measurement of collateral function

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Background: A valid angiographic characterization of collaterals would be of clinical relevance for the evaluation of new therapeutic modalities to induce collateral growth. These semiquantitative angiographic gradings require a validation through invasive parameters of collateral function.
Methods and Results: In 78 patients with total chronic occlusion (TCO) of a major coronary artery (duration>2 weeks) collaterals were assessed angiographically according to their anatomical location, the apparent size of the visible collateral connection (grade 0 no continuous connection, 1 fathom-like continuous connection, 2 side-branch-like connection), and the criteria of recipient segment filling (Rentrop grading). Collateral function was quantitatively assessed by simultaneous Doppler flow (average peak velocity APV) and coronary pressure (PD) recording distal to the occlusion before recanalization. A collateral resistance index (RColl) was calculated. After antegrade flow was restored for at least 30 minutes recruitable collateral flow was measured during a final balloon inflation. There was no difference in RColl with respect to the anatomical location. Rentrop grade 3 filling was associated with a lower RColl than grade 2 (5.79±2.21 vs. 9.66±6.47 mmHg/cm/s; p=0.011). The 3 collateral connection grades could discriminate collaterals with distinctly different collateral function (0: 14.71±7.27; 1: 7.75±4.42; 2: 5.07±2.22 mmHg/cm/s; p<0.001). Also the recruitable collateral function was better preserved in collateral connections of grade 2 with a lower RColl (0: 34.33±20.41; 1: 18.78±12.08; 2: 8.96±5.16 mmHg/cm/s; p<0.001).
Conclusions: The collateral size, and not the anatomical location, is the best predictor of collateral function. Side-branch like sized collaterals are also those which remain immediately recruitable after recanalization of a TCO, whereas smaller collaterals may not provide protection during acute reocclusion.

P482 Intravascular elastography detects the weak vulnerable plaque

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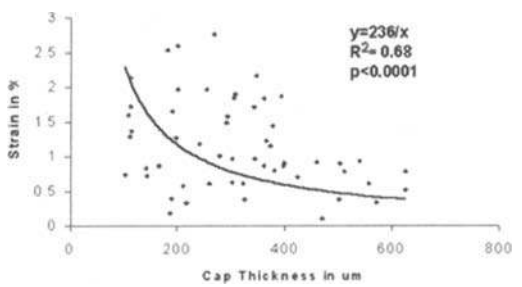
The cap of a vulnerable plaque is the weakest link, which can rupture due to increased strain. Intravascular elastography is a new technique to measure local strain in a plaque. Finite element modeling of cap thickness related to stress showed an inverse relationship between these components. Since stress and strain are closely related, a relationship between strain and cap thickness should exist.
Methods: Coronary artery specimens, collected after autopsy, were evaluated for their morphological properties in a water-tank at different intraluminal pressures (80 and 100 mm Hg)with standard intravascular ultrasound catheters and an elastographic workstation.
Selected segments were stained on the presence of collagen and fat, smooth muscle cells and macrophages. In histology a vulnerable plaque was defined as plaque with a thin cap with moderate/heavy macrophage infiltration and a plaque that consisted for at least 40% of atheroma. In elastography, vulnerable plaque was defined as a high strain region on the surface of the plaque with an adjacent low strain region.
Results: In 24 diseased coronary arteries, we studied 54 crossections. 23 vulnerable plaques and 31 non-vulnerable plaques were found in histology. The relation between cap thickness and strain is inverse. A curve estimation, based on finite element modeling, showed a R^2=0.68 with a p <0.0001 (see fig). It should be notified that a cap > 400 μm results in a strain < 1%, while the data are more scattered for lower cap thickness.



Relation strain vs. cap thickness.

Conclusion: Intravascular elastography detects high strain regions in vulnerable plaques, which correlate with the thickness of the cap of plaques. This is the in vitro proof of a former described finite element model on human coronary vessels.

P483 What is the pathophysiological significance of myocardial bridging in patients with chest pain but normal coronary arteries?

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Background: Myocardial bridging (MB) is occasionally observed by coronary angiography in patients with chest pain despite having normal coronary arteries. However, the pathophysiological significance of MB is unclear. Therefore, we investigated whether the occurrence of MB was associated with any clinical or angiographic parameters, in such patients. Methods: One hundred fourteen patients with chest pain despite having normal coronary arteries were evaluated. On echocardiography, the left ventricular mass index (LVMI) was calculated according to the formula of Devereux and Reichek, and left ventricular hypertrophy was defined as on LVMI >110 g/m^2 for women and >134 g/m^2 for men. On coronary angiography, a spasm-provocation test was performed by infusing acetylcholine into the left coronary artery. The test result was defined as positive when the diameter of the coronary artery decreased by 50% and ST segment changes were documented. MB was defined as a >15% reduction in coronary arterial diameter during systole after intracoronary injection of nitroglycerin. The patients were divided into two groups based on whether MB was present (Group I) or not (Group II). Results: MB was observed in 41 patients (36%) (Group I) and was located at the mid-segment of the left anterior descending coronary artery in all of them. The percentage of men was greater (Group I 78% vs. Group II 45%: p = 0.0007) and the body mass index was smaller (Group I 23.6±0.3 vs. Group II 25.1±0.4: p = 0.0169) in Group I than in Group II. LVH tended to be less common in Group I (29% vs. 47% in Group II: p = 0.0707). Coronary spasm was induced more frequently in Group I (30/41, 73%) than in Group II (29/73, 40%) (p = 0.0006). Multivariate regression analysis using these factors demonstrated that a positive spasm-provocation test (p = 0.0035) and male gender (p = 0.0037) were associated with the presence of MB
Conclusions: These results suggest that MB correlates with a positive spasm-provocation test, independently of gender difference, in patients with chest pain despite having normal coronary arteries. Thus, MB may increase the risk of coronary spasm in such patients.
3

P484 Haemodynamic effects of aqueous nitric oxide solutions applied directly into human coronary circulation

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In saline perfused isolated heart models nitric oxide (NO) has been shown to dilate vessels and to inhibit platelet function, both effects highly desirable during percutaneous intervention (PCI) in patients with coronary artery disease (CAD). Whether or not NO applied directly into human coronary circulation exerts biological effects is unknown so far. Therefore, the aims of our study were: (i) to develop a method for reproducible production of sterile solutions containing authentic NO, (ii) to find a save mode of intracoronary (ic.) application, and (iii) and to characterize potential dilatory effects in conduit and resistance coronary arteries. Methods: Changes in coronary blood flow (CBF) were quantified by quantitative coronary angiography (QCA) and intracoronary Doppler guide wires (ICD) in 13 patients without flow limiting CAD after application of either saline controls, aqueous NO solutions (NO,1 – 6 μmol), adenosin (ADO, 2.4mg/min) or isosorbiddinitrate (ISDN, 0.3 mg) in random order. Results: NO dilated epicardial arteries in a dose-dependent manner up to 10+1%, equivalent to that seen upon ISDN. In parallel average peak velocity (APV) increased from 21 to 51+4 cm/s. Thus NO dilated coronary microvasculature to almost the same degree as seen after infusion of adenosine, whereas ISDN increased APV only slightly. Consequently, coronary blood flow increased according to the following rank order: NO and ADO > ISDN, whereas saline controls were without effect. Surprisingly, NO induced increases in CBF lasted much longer than expected from its biochemical life span in human blood. Systemic parameters such as heart rate or blood pressure remained unaffected after ic. application of aqueous NO solutions. Conclusions: Aqueous NO solutions can be applied directly into human coronary circulation and dilate uniformly epicardial and resistance arteries increasing coronary blood flow severalfold. These findings offers the avenue to selectively increase local NO stores within the coronary circulation without exerting systemic side effects, representing a new and attractive approach during percutaneous coronary interventions in patients with CAD.

P485 Impaired dilator response to atrial natriuretic peptide of coronary resistance vessel in patients with hyperinsulinaemia

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Background: Hyperinsulinemia (HI) was suggested as one of risk factors in coronary artery disease. We investigated whether functional abnormality exists in coronary reactivity in HI without any significant coronary stenosis.
Methods: We performed 75g oral glucose tolerance test (OGTT) and coronary flow study in 32 patients with angiographically normal coronary arteries. Epicardial artery vasoactivity to acetylcholine was used to assess endothelial function. Coronary blood flow responses were evaluated by intracoronary Doppler flow velocity recordings and quantitative angiography. HI was diagnosed as a fasting serum concentration exceeding 20mU/L or as a peak serum concentration exceeding 150mU/L during the OGTT. 50ug of adenosine triphosphate (ATP), 1mg of isosorbide dinitrate (ISDN) and 0.05mg/kg of atrial natriuretic peptide (ANP) were intracoronary administered in the middle segment of left anterior descending coronary artery in patients with HI (N=10, 57± 8yrs, 5 males) and normoinsulinemia (NI) (N=22, 61±7yrs, 16 males).
Results: Arterial blood pressure was not changed during the study. Epicardial artery vasoactivity to acetylcholine was reduced in HI, but statistically not significant. Resting average peak velocity (APV) and coronary flow reserve with ATP (13.6±3.8 cm/s, 3.1±0.9) were similar to HI group (12.5±2.2cm/s, 3.3±0.4). In NI group, APV with ISDN (37.6±8.7cm/s) and ANP (36.3±9.7cm/s) were similar. In contrast, APV with ANP (27.6±10.2cm/s, $p<0.001$) was significantly blunted compared to ISDN (40.0±10.5cm/s) in HI group. Epicardial artery vasoactivity to ISDN and ANP did not differ between the two groups.
Conclusion: These results indicate the impaired dilator response to ANP not ISDN on coronary resistance vessel in HI. ANP receptor may be impaired even in the stage of mild endothelial dysfunction in HI.

CONGENITAL HEART DISEASE IN GROWN UP

P486 Pulmonary artery root dilatation in Marfan syndrome: quantative assessment of an unknown criterion

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Background: Dilatation of the main pulmonary artery is one of the established criteria for the diagnosis of Marfan syndrome. However, the prevalence and prognosis of pulmonary artery dilatation in Marfan syndrome is still unknown. Purpose of this study was to assess main pulmonary artery dimensions in normal subjects and in patients with Marfan syndrome.
Methods: Fifty Marfan patients (mean age 33 (10) years, 34 men, 16 women) and 15 matched control subjects (mean age 28 (4) years, 9 men, 6 women) underwent cardiac magnetic resonance imaging. Pulmonary artery dimensions were obtained on axial spin echo images at two different levels: 1) the level of the pulmonary artery root, and 2) the level of the pulmonary artery bifurcation.
Results: Upper limits of normal (mean + 2 SD) at the pulmonary root and at the pulmonary artery bifurcation were 34.8 mm and 28.0 mm, respectively. Pulmonary artery dilatation was demonstrated in 37 (74%, root) and 38 (76%, bifurcation) of the 50 Marfan patients. There was a good correlation between pulmonary and aortic root diameter in non-operated Marfan patients ($r=0.76$). Dimensions of pulmonary root were larger (38.4 mm, range 28.3 - 50.7 mm) than dimensions at the pulmonary bifurcation (30.7 mm, range 21.4 - 38.5 mm, $p<0.001$). Marfan patients with aortic root replacement (n=35, root 39.7 mm, bifurcation 31.7 mm,) had significantly larger pulmonary artery dimensions than non-operated Marfan patients (n=15, root 35.5 mm, bifurcation 28.5 mm, $p<0.01$).
Conclusion: In the majority of Marfan patients the main pulmonary artery, particularly the pulmonary root, was dilated. Pulmonary artery dimensions were significantly larger in Marfan patients with aortic root replacement than in non-operated Marfan patients. These findings suggest that dilatation of the pulmonary root increases with progressive involvement of the cardiovascular system in Marfan patients. Although, until now, main pulmonary artery aneurysm and dissection are rare, they may become of more clinical relevance in the near future because of increased longevity in Marfan patients.

P487 Pregnancy among women with ASD: objective versus subjective quality of life

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Background: The long-term outcome after surgical ASD closure in childhood studied in our "Rotterdam Quality of life" study is excellent. There are no cardiac-related deaths and we found a very low morbidity after long-term follow-up. As the female patient enters adulthood, questions arise on the different aspects of pregnancy.
Aim: The purpose of this study is to analyse pregnancy data of women with ASD closure compared to the normal Dutch population.
Methods: We investigated the long-term outcome (20-35 years) of a cohort of 90 consecutive patients operated in the period 1968-1980 in our centre, with ASD closure in childhood (< 15 years) with respect to pregnancy and psychological aspects concerning pregnancy and compared these results with the Dutch population.
Results: From the 53 female patients participating in the study, 27 patients had child(ren) (50.9%). In total there were 69 pregnancies, which resulted in the birth of 50 children, 18 miscarriages and 1 abortion. One child was born with congenital heart disease (ASD). Pregnancy data of the normal Dutch population is derived from the Central Bureau for Statistics (CBS). In table 1, percentages of first successful pregnancy are shown for both female ASD patients and the Dutch female population.

Age (yr.)	<24	25-29	30-34	>35	Total
ASD	3.8%	32.0%	15.1%	0%	50.9%
CBS	13.4%	30.4%	27.7%	8.5%	80%

Of the 26 female patients who had not had children, 14 (54%) had negative expectations for having children in the future. Of all female patients, 25% felt their heart defect to be a limiting factor in having children; the greatest concern was that their offspring also would have a congenital heart defect. Of the 37 male patients, only 35% had child(ren) until now.
Discussion: Only 50.9% of our female patients had children compared to 80% in the normal Dutch population ($p<0.0001$). Since the objective health is very good, psychological aspects may play an important role in this striking difference in occurrence of pregnancy, especially the fear for congenital defects in the offspring seems important and needs further attention. Conclusion: Although the survival and long-term physical outcome is excellent after surgical closure of ASD at young age, psychological barriers exist, resulting in significantly less pregnancies than expected.

P488 Mid-term follow-up of haemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of Fallot

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Background: Pulmonary regurgitation (PR) late after total correction for tetralogy of Fallot may lead to progressive right ventricular (RV) dilatation and an increased incidence of severe arrhythmias and sudden death. Pulmonary valve replacement (PVR) long after repair of Tetralogy of Fallot (TOF) leads to rapid improvement of RV function. Whether further improvement after 6 months from PVR occurs, is unknown. In this study, magnetic resonance imaging (MRI) was used to assess the effect of PVR on RV function and PR up to 18 months after PVR.
Methods and Results: Nineteen consecutive adult patients who underwent PVR in our institution between 1998 and 2001 were studied. Median age at initial repair was 5.0 ± 4.2 years (range 0.4 to 21.0) and median age at PVR was 29.2 ± 9.0 years (range 17.0 to 45.6). Cardiac MRI was performed 6.1 ± 3.4 months before and 7.9 ± 2.4 months and 13.8 ± 5.9 after PVR. Preoperative PR was 46% (range 25-64%). After PVR, 4 out of 19 patients (21%) showed mild residual PR. One year later, 6 out of 19 (32%) patients had mild PR. RV end-diastolic volume (RVEDV) decreased from 308 ± 99 ml to 206 ± 53 ml ($p<0.001$) to 193 ± 54 ml ($p=0.25$) and RV end-systolic volume (RVESV) decreased from 177 ± 70 ml to 113 ± 37 ml ($p<0.001$) to 103 ± 36 ml ($p=0.12$). RVEF increased slightly from 44 to 45 to 49% (not significant).
Conclusion: In adult patients late after total correction of TOF, improvement of right ventricular function is predominantly achieved in the first year after PVR.

P489 Right ventricular function before and after pulmonary valve replacement in adults late after repair of tetralogy of Fallot

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Background: Pulmonary regurgitation (PR) late after total correction for tetralogy of Fallot (TOF) may lead to progressive right ventricular (RV) dysfunction and an increased incidence of severe arrhythmias and sudden death. Timing of pulmonary valve replacement (PVR) is subject to discussion since the effect on RV function in adults is unclear.
Purpose: In this study, magnetic resonance imaging (MRI) was used to assess the effect of PVR on RV function and PR. Clinical improvement was established by means of the NYHA classification
Methods and Results: 26 Adult patients who underwent PVR in our institution between 1998 and 2001 were studied. Median age at initial repair was 5.0 ± 4.2 years (range 0.4 to 21.0) and median age at PVR was 29.2 ± 9.0 years (range 17.0 to 45.6). Cardiac MRI was performed at a median of 5.1 ± 3.4 months before and 7.4 ± 2.4 months after PVR. Mean preoperative PR was 46 ± 10% (range 25-64%). After PVR, 20 out of 26 patients (77%) showed no residual PR, one patient had moderate residual PR and 5 patients mild PR. RV end-diastolic volume (RVEDV) decreased from 305 ± 87 ml to 210 ± 62 ml ($p<0.001$) and RV end-systolic (RVESV) decreased from 181 ± 67 ml to 121 ± 58 ml ($p<0.001$). No significant change was found in RV ejection fraction (RVEF) (42 vs. 42%). We introduced a new method to correct RVEF for regurgitations and shunting (RVEFcor=pulmonary forward flow-pulmonary regurgitation (ml)/RVEDV). This parameter increased from 25.2 ± 8.0% to 43.3 ± 13.7% ($p<0.001$). Mean validity class increased from 2.0 to 1.3 ($p<0.001$).
Conclusion: In adult patients with PR and RV dilatation, late after total correction of TOF, RVESV decreased and RVEFcor increased dramatically, indicating an overall improvement of RV function. This is in accordance with our finding of improved validity. We therefore advocate a less restrictive management concerning PVR.

P490 QRS duration at rest predicts maximal exercise performance in adult patients with repaired tetralogy of Fallot

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Background: A right bundle branch block (RBBB) is found in most of the patients with repaired tetralogy of Fallot (TF). When the QRS complex exceeds 180 ms or prolongs progressively over time, the incidence of sudden cardiac death increases. We wondered if QRS duration could predict maximal exercise capacity (Wmax, Watt) or maximal oxygen consumption (peak VO2, ml/min).
Methods: Thirty five TF patients with RBBB were examined. QRS duration on V1 (ms)was measured at rest. The right ventricular diameter in parasternal and apical short axis were measured by transthoracic echocardiography. Via color Doppler pulmonary and tricuspid regurgitation (scale 0-4/4) were quantified. Wmax and peak VO2 were obtained during a bicycle stress test (protocol: 20 Watt + 20 Watt/min). Cardiac output (CO, l/min) at rest and at 100 W were measured by CO2 rebreathing. Stroke volume (SV, ml) was calculated. Simple linear regression analysis was used to describe the correlation between QRS duration and Wmax, peak VO2, CO and SV. Multiple linear regression analysis was used to identify the continuous independent variables obtained by echocardiography and influencing the QRS duration. Kruskal Wallis test was performed to evaluate the relation of the nominal echocardiograhic variables on QRS duration. Statistical significance was defined as $P<0.05$.
Results: Thirty patients (25 male, 5 female; age 25±7 y, mean±SD) were selected; five patients could not pass the anaerobic threshold and were excluded. The right ventricular dimensions (parasternal and apical short axis) were 2.7±0.5 cm and 3.8±0.8 cm, respectively. QRS duration, Wmax and peak VO2 were 156±20 ms, 194±49 Watt and 2191±576 ml/min, respectively. QRS duration correlated with Wmax and peak VO2 ($R^2=0.35$ and $R^2=0.18$, respectively, $P<0,05$). The apical short axis diameter of the right ventricle was identified as a predictable variable of QRS duration. No significant correlation was found between the severity of pulmonary or tricuspid regurgitation and QRS duration. No significant correlations were found between CO at rest and at 100 W (4.6±1.6 and 16.6±3.7 l/min, respectively) and QRS duration. QRS duration and SV at 100 W (134±31 ml) were correlated positively ($R^2=0.55$, $P<0.05$).
Conclusions: Adult patients with repaired TF and RBBB have a reasonable exercise performance. QRS duration itself seems to be a strong predictor of maximal exercise capacity. We suggest that earlier activation of the left ventricle in repaired TF patients can result in maintenance of the exercise tolerance. Further investigation is planned to confirm this hypothesis.

P491 QRS-width longitudinally measured in congenital heart disease

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Background: ventricular arrhythmias play a major role in the morbidity and mortality of patients after surgical correction of congenital heart defects. From the literature it is known that QRS-width is a predictor for ventricular arrhythmias in patients with corrected tetralogy of Fallot. If this is true for other congenital defects is not known. Also the changes over time in the QRS-width may be an important factor in the prediction of these arrhythmias.
Methods: A cohort of 351 patients with diagnosis ASD, VSD, PS, tetralogy of Fallot and transposition of the great arteries is longitudinally studied. All patients were operated in childhood (<15 yr.) in our centre, between 1968 and 1980. Mean age at operation was 5 yr., with a mean follow-up of 26 yr. The QRS-width is measured in 1990 and in 2000.
Results: QRS-width changed from mean 101 (range 60-200) in 1990 to 113 (range 70-200) in 2000.In the tetralogy of Fallot group the increment was larger then in the other groups. Sustained ventricular tachyarrhythmias occurred in 5% between 1990 and 2000, also more in the tetralogy of Fallot group (see table).

	ASD	VSD	PS	TGA	ToF
Number of pts	91	95	37	51	77
QRS 1990 (msec)	88	100	94	95	121
QRS 2000 (msec)	97	113	108	110	137
QRS-increment	9	13	14	15	16
VT '90-2000(%)	4.4	2.1	2.7	7.8	9.1
Mort'90-2000(%)	1	4	3	4	3

Conclusion: QRS-width increases over time, but there were clear differences in the different diagnosis groups of patients with congenital heart disease. In the ASD-group the QRS-width-increment is significantly less, and in the tetralogy of Fallot patients the QRS-width-increment is more pronounced ($p=0.004$). A relation was found between QRS-width-increment and the occurrence of sustained ventricular tachyarrhythmias.

P492 Ventilatory response and pulmonary gas exchange at rest and during exercise in patients after the fontan operation

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Background: Although abnormal pulmonary circulation, lung function and respiratory response during exercise are well known characteristics in Fontan patients, the relationships between these impaired functions have not been well established.
Methods and Results: Pulmonary function and cardiopulmonary exercise tests were performed in 95 Fontan patients (mean age = 13.6 years, atriopulmonary connection in 29, total cavopulmonary connection in 66) and 44 controls. Vital capacity (VC) and diffusion capacity were significantly lower in Fontan patients than in controls. VC was associated with the number of surgical procedures and decreased significantly during follow-up, being significantly related to the higher frequency and smaller tidal volume (respiratory pattern) during exercise, while did not relate to the dead space ventilation (VD/VT), ventilatory equivalent for CO2 production (ventilatory efficiency) or peak oxygen uptake. Rest and exercise minute ventilation was accelerated and the VD/VT was higher during exercise in Fontan patients. Lower arterial saturation was related with accelerated ventilation, resulting lower resting PaCO2 and resting arterial gas tensions and alveolar ventilation to CO2 production ratio, not the types of repair or VC, determined PaO2 and PaCO2 dynamics during exercise. Fontan patients with left ventricular type had higher diffusion capacity, superior ventrilatory efficiency and peak oxygen uptake compared with those without.
Conclusions: After the Fontan operation, progressive restrictive ventilatory impairment determines the exercise respiratory pattern. Resting slight but significant hypoxia and high VD/VT during exercise have a great impact on accelerated ventilation. However, the ventricular morphology rather than the lung volume or respiratoty pattern have a greater impact on not only their exercise capacity but exercise ventilatory efficiency.

P493 Quality of life of long-term survivors after Fontan operation for tricuspid atresia: a national study

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Introduction: between 1972 and 1990 86 patients with tricuspid atresia underwent Fontan surgery in The Netherlands. 20 Years survival is 66%. What are the consequences for daily life of the long-term survivors?
Aim of the study: to measure subjective health status and health related quality of life (HRQOL) as well as vocational situation late after surgery (follow-up at least 12 yrs).
Material and Methods: of the 86 patients 29 died and 2 were lost to follow-up. Of the remaining 55 (mean follow-up 20.5 yrs) 27 (15-44 yrs, mean 26.7 yrs, median 26 yrs, 15 male) participated in the study by returning completed SF-36 and TAAQOL (HRQOL with subjective view on physical, emotional, cognitive and psychosocial functioning) questionnaires.
Results: significant lower scores for SF 36 role functioning emotional ($p<0.05$) and physical functioning, role functioning physical, vitality, general health perceptions, social functioning, mental health (all $p<0.001$) were found. Also compared to norm values the TAAQOL showed only significant lower values for vitality ($p<0.05$) and gross motor functioning ($p<0.001$). 37% had a paid job, working more than 15 hrs per week. 41% had complete unemployment benefit.
Conclusion: long-term survivors of Fontan surgery experience a limited health status, but a satisfying subjective quality of life. Employment figures are disappointing. Improved counselling aiming at highest education possible is important and vocational guidance is mandatory.

P494 Cardiorespiratory function in patients with Eisenmenger syndrome

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Interpretation of cardiopulmonary exercise testing (CPET) in patients with secondary pulmonary hypertension still needs to be elucidated. We evaluated the influence of anemia, reduced ventricular function and pulmonary function on exercise tolerance.
Method: 21 Patients (P) (29.2±8.1 y, 13f, 8m) performed a progressively increasing work rate (WR) (10Watt/2min) CPET to maximum tolerance. Maximum oxygen uptake (PeakVO2), WR, ratio of O2 uptake toWR increase (DVO2/DWR), ventilatory efficiency (ventilationVE/VCO2; VE/ VO2) and minimal O2 saturation during exercise were calculated These parameters were correlated with mean corpuscular haemoglobin concentration (MCH) haemoglobin, haematocrit and with forced vital capacity (VC) and forced expiratory volume (FEV1).
Results: No adverse events occurred. 3 P with echocardiographically assessed severely reduced ventricular function had a significantly reduced PeakVO2 (10.1±1.1 vs 15±2.8ml/kg/min,p=0.018) and DVO2/DWR (20 Watt)(4.9 ±0.6 vs15.3±4.6mlO2/Watt; p=0.009).In P (n=5) with anemia (MCH<28pg) had a significantly reduced PeakVO2 (12.3±1.5 vs 15.1±3.2ml/kg/min,p=0.017), maximum WR (28.8±8 vs. 43.1±16.6 Watt; p=0.02) minimal saturation during exercise (62.8±6.8 vs. 74.1±12.7%: p=0.039). VE/VO2 was significantly increased (49.4±9.9 vs. 35.8±12;p=0.017) whereas DVO2/DWR (20Watt) was not significantly reduced. All P had a slightly reduced VC (67.2±16.7%) and normal FEV1 (72.7±12.7%). Both did not correlate with PeakVO2, WR, DVO2/DWR.
Conclusion: PeakVO2 is manly determined by ventricular function and anemia. DVO2/DWR (20Watt) may be helpful in differentiating both entities. Slightly to moderately reduced pulmonary function does not effect O2-uptake.

P495 Carotid and femoral intima-media thickness in adult patients succesfully operated for aortic coarctation

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Objectives: Structural changes and abnormal vascular reactivity persist in patients with aortic coarctation despite successful repair. This may be due to previous increased blood pressure in the pre-coarctatial arterial conduits and contributes to the increased late morbidity and mortality in post-coarctectomy patients. B-mode ultrasound imaging can describe status and changes in intima-media complex thickness (IMCT) of carotid and femoral arterial walls. Carotid and femoral IMTC was investigated in normotensive adult post-coarctectomy patients.
Methods: Carotid and femoral IMTC was measured in 26 normotensive (31.7(SD9.1)yrs) successfully operated post-coarctectomy patients. Mean age at operation was 9.5(range 0.8-22.1) years. Normotension was defined as a daytime mean systolic blood pressure under 140mmHg as registered on 24 hour ambulatory blood pressure monitoring. Patients were compared to 26 age and sex matched controls (33.9(9.9)years). A subject's IMTC was defined as the averaged measurements of three right, three left carotid, and two left and two right femoral arterial wall segments. In comparisons of the carotid and femoral arterial IMTC's between patients and controls, the averaged per subject IMTC measurements of each of the arterial conduits were used. Comparisons were done with unpaired Student t-tests.
Results: Overall IMTC of the normotensive post-coarctectomy patients (0.65(0.17)mm) was increased if compared to controls (IMTC=0.59(0.11) mm): DIMT=0.06mm, p=0.002. Carotid IMTC was 0.70(0.10)mm in patients and 0.60(0.09)mm in controls: DIMT= 0.14mm, $p<0.0001$; however the femoral IMTC's were similar: (0.56(0.10)mm in patients and 0.57(0.07)mm in controls: DIMT=0.01mm, p=0.64.
Conclusions: Normotensive, post-coarctectomy patients presented with increased carotid IMTC, where the femoral IMTC is similar to controls. It may be concluded that the vascular damage in post-coarctectomy patients is more apparent in the vascular bed proximal of the former aortic coarctation. This finding reflects the increased risk for cardiovascular and cerebral events in these patients. Moreover, the results illustrate the need to investigate multiple vascular beds according to a standardized protocol in order to describe mechanism of disease and improve disease prevention in those at vascular risk.

P496 Exercise-testing for the detection of hypertension in adult post-coarctectomy patients

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Objective: Successfully operated aortic coarctation patients frequently show a marked systolic hypertensive blood pressure reaction at exercise. In view of this typical hemodynamic pattern, the question is warranted whether blood pressure in daily life is normal when office readings are low. We therefore determined whether exercise-testing in presumed normotensive adult patients after successful repair of aortic coarctation can predict hypertension at 24 hour blood pressure measurement.
Design and Methods: Seventy-three presumed normotensive, successfully repaired, adult post-coarctectomy patients (44 male; mean age 30, range 17-53 years; time after operation 22.9 years, SD 7.4) underwent a maximal, symptom limited treadmill exercise test (Bruce protocol). Blood pressure (BP) was measured every 3 minutes by conventional RRK. Daytime BP (7:00-23:00) was assessed by 24 hour ambulatory BP monitoring (Spacelabs 90207). Patients were considered hypertensive when day mean systolic BP was above 140 mmHg. A ROC-curve was constructed using maximal systolic BP during exercise as test variable.
Results: Seventeen patients (23%) had daytime hypertension. Analysis of the ROC-curve (area 0.789) revealed that in our patients a cut-off value of maximal systolic BP during exercise above 188 mmHg had the highest sensitivity (82%) and specificity (71%). Using day time BP above 135 mmHg as cut-off value, did not result in significant better test characteristics (area 0.806).
Conclusions: Hypertension is a common finding even in presumed normotensive and successfully corrected adult post-coarctectomy patients. Exercise-testing can predict hypertension in the absence of 24 hour ambulatory blood pressure measurement, however sensitivity and specificity are not very high. 24 hour ambulatory blood pressure measurement should be regularly performed for early detection of hypertension in these patients, who already are at high risk for cardiovascular complications.

P497 Left ventricular remodelling and mechanics after successful repair of aortic coarctation. Correlation with blood pressure on exercise and ambulatory blood pressure measurement

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A good surgical repair of aortic coarctation (AoCo) does not always protect from persistent systemic hypertension and left ventricular (LV) remodelling. In 52 normotensive patients (mean age 21.1 ± 10.5; range 2-40 years) followed up after a successful repair of AoCo (mean age at coarctectomy 11.8 ± 10 years), we evaluated the LV remodelling, endocardial and midwall mechanics by echo-Doppler, the trans-isthmic gradient and the systemic blood pressure at rest/exercise and during ambulatory blood pressure monitoring (ABPM), in order to identify factors that might predispose to persistent abnormalities. Cut-off levels for LV mass index (Mi) and relative wall thickness (RWT) were defined to assess LV geometry. The smallest diameter of the aorta was assessed by magnetic resonance imaging (MRI) and calculated as percent narrowing compared with the diameter of the aorta at the diaphragmatic level. The echocardiographic findings were compared with those of 142 controls (N).
In the AoCo group LV end-diastolic volume index (EDVi), Mi, M/V ratio were increased. The LV systolic chamber function estimated at endocardial (VCFc) and midwall (mwVCFc) level was increased. The LV contractility estimated at endocardial level was increased (Z-score > 95° percentile) in 13/52 (25%), whereas that at midwall remained elevated in 10/52 (21%) patients. Twenty-seven (52%) patients had normal LV geometry; among the other 25 with abnormal geometry, 4 (8%) had a pattern of concentric remodelling, 18 (34%) an eccentric hypertrophy and 3 (6%) a concentric hypertrophy. Compared with those with abnormal LV remodelling, the patients with normal LV geometry are younger, had earlier surgical repaired, have lower systolic blood pressure rest/exercise and during ABPM. Mi, M/V ratio and RWT showed a significant positive correlation with age, age at surgical repair, systolic blood pressure on rest/exercise and ABPM ($p < 0.01$). These parameters are predictive of abnormal LV remodelling by multivariate analysis. In conclusion normotensive patients after successful surgical repair of AoCo may have persistent abnormal LV geometry and a hyperdinamic state. These persistent abnormalities are more frequent in those who have undergone to late repair and who exhibit an elevated systolic blood pressure on rest/exercise and ABPM.

P498 Hypertrofic adaptation of the right ventricle seems important for exercise performance in mustard patients

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Background Previously, transposition of the great arteries (TGA) was treated by atrial switch procedures after which the right ventricle served the systemic circulation. Although patients who have undergone such interventions are generally considered asymptomatic, it is well established that their exercise performance is below normal values. It is uncertain, whether the ability of the right ventricle to adapt to the systemic blood pressure by myocardial hypertrophy influences exercise performance. The aim of the present study was to compare right ventricular myocardial mass (RVM) with maximal oxygen consumption (VO2max) in patients with TGA corrected by the Mustard procedure.
Patients and methods: Seventeen unselected patients (16 males and one female), age (median (range)) 19 (10 - 29) years, were examined 18 (9 - 25) years after Mustard's procedure for TGA (age at operation 14 (10 - 48) months). RVM was measured by magnetic resonance imaging using breath-hold cinematographic gradient-echo technique with the imaging plane in the true short axis of the right ventricle (slice thickness 6 mm, no inter-slice gaps, TR 55 msec). VO2max was determined by an individualized incremental bicycle ergometer test with continuous measurement of metabolites. Criteria for maximal exercise were exhaustion, VO2 plateau reached or VCO2/VO2 > 1.1.
Results RVM index was (mean (SD)(range)) 94.5 g/m^2 (16.9) (56.3 - 120) and VO2max was 1.90 l/min (0.73) (= 31.6 ml/min/kg (6.95)). Furthermore, we found a positive correlation between RVM index and VO2max ($r = 0.57$, $p = 0.02$).
Discussion In contrast to left-sided ventricular systolic dysfunction, where the degree of myocardial hypertrophy correlates with the severity of heart failure, this study indicates that increased RVM index after atrial switch procedures for TGA results in better ventricular function as measured by exercise performance. However, it is uncertain what causes the large range in RVM index in Mustard operated patients. One explanation could be the angiotensin-converting-enzyme genotype, which is known to be related to the degree of myocardial hypertrophy in other settings of increased ventricular workload.

EVALUATION OF THE RESULTS OF CARDIAC SURGERY

P499 Two-years clinical and angiographic follow-up after a traumatic coronary artery bypass

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Atraumatic Direct Coronary Bypass (ACAB) is a challenging, quickly developing surgical technique, by which the internal mammary artery (LIMA) is harvested and anastamosed to the left anterior descending artery (LAD), resulting in a minimal cardiothoracic procedure, smaller number of in-hospital complications, and better patients outcome.
A total of 200 patients with anginal symptoms of CCS 2.7 ± 0.4, and significant LAD disease, who underwent coronary artery bypass grafting (with the use of thoracoscopically harvested LIMA) at the 1st Department of Cardiac Surgery since 1998, were included to prospective follow-up study.
Preliminary results comprise 79 patients, who underwent clinical and angiographic control(mean observation period was 1.5 year). Major adverse coronary events were observed in 5 patients (6.3%), and included: myocardial infarction (1 patient, 1.2%), aggravation of anginal status(4 patients, 5.0%). We noted one death due to disseminated neoplasmatic disease, no neurologic event was noted. An avarage patients anginal status was CCS I, ECG excercise test was negative in 64 patients (81%), positive in 13 patients (16.4%), 4 patients were not able to perform stress test due to sceleto-muscular disorders. Seventy eight patients (98%) stated their quality of life as very good and good. Angiographic control of LIMA-LAD graft anastamosis was performed in 72 patients (91%). Patency of grafts was evaluated with the use of Fitz-gibbon scale: 64 patients (88%) had full patency of the graft (score A), in 4 patients (5.5%) we found stenosis reducing distal anastamosis of the trunk more than 50% (score B), only 2 patients (2.7%) had totally occluded grafts (score 0), one was treated with PTCA of LAD. Coronary artery disease progression was observed in 14 patients (19.4%) who were treated with PTCA.
Conclusions: Excellent long term clinical and angiographic results can be achieved with ACAB technique. ACAB is safe and effective method of treatment in proximal LAD lesions, thus it may be the treatment of choice in patients with a high risk of stent restenosis. We believe, that with increasing surgery experience, ACAB approach will have a major impact on the management of coronary patient with type B or C lesion of LAD.

P500 Impact of left anterior descending flow and collateral circulation on myocardial ischaemia during minimally invasive coronary surgery

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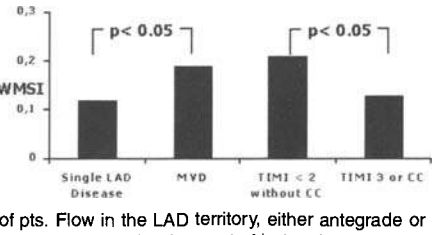
Background: Concern has been raised about the effects of ischemia following prolonged left anterior descending (LAD) coronary artery occlusion during minimally invasive direct coronary artery bypass surgery (MIDCAB). In order to evaluate the impact of collateral circulation (CC) and the extent of coronary artery disease on intraoperative ischemia, myocardial function was monitored by intraoperative transesophageal echocardiography.
Methods: Among 92 patients (pts) (80 males, median age 62, range 45-84 years) Wall Motion Score Index (WMSI) was calculated before (baseline), during occlusion and after LAD reopening.
Results: LAD occlusion lasted 22±6min. Contractile impairment began 3.6±2.6min after LAD occlusion. Recovery was documented 4.2±2.1min after reopening. WMSI increased from 1.34±0.32 to 1.48±0.36 ($p<0.001$) during LAD occlusion, and was reverted after LAD reopening (1.30±0.32, $p<0.001$ vs occlusion and p=NS vs baseline). One hour after LAD reopening, contractility was ameliorated in 10 pts (11%), unchanged in 53 pts (58%) and worsened in 28 pts (31%) compared with baseline findings. In all 28 pts with worsened post ventricular function, a 48 hours transthoracic echocardiography documented functional recovery. DWMSI (deterioration in WMSI occlusion over baseline) was related both to the extent of coronary artery disease (MVD=multivessel disease) and the status of coronary flow in the LAD and in CC (Figure 1).
Conclusions:
During MIDCAB with LAD occlusion, anterior wall dysfunction is transient with prompt recovery after completion of the anastomosis. However, myocardial stunning can be documented in a minority of pts. Flow in the LAD territory, either antegrade or retrograde, appears to protect against the development of ischemia.



P501 New evaluation for coronary artery bypass surgery using Doppler guide wire – effect of left internal thoracic artery graft

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Back Ground: Now we can find a lot of reports about the effects of PTCA for native coronary arteries using a doppler guide wire. However there were no reports about coronary flow reserve(CFR) of native coronary artery before and after coronary artery bypass surgery (CABG). It was estimated only by angiography. The purpose of this study is to evaluate physiologically the efficacy of left thoracic artery (LITA) graft for left anterior descending artery (LAD) before and after CABG with a doppler flowire. Methods: Intracoronary flow verosity was measured at the distal to the target lesion of LAD before CABG and three weeks after operation phasic flow verosity recording were obtained in the native LAD using doppler guide wire in 22 patients who underwent LITA grafting to the LAD. The average peak verosity (APV) and CFR defined as the ratio of APV during hyperemia (10mg of intracoronary papaverine) versus APV at baseline were obtained during Flo Wire measurements. Results: All patients had an uneventful postoperative course. LITA graft had a good patency in 22 cases. CFR of LAD significantly increased from 1.61±0.54 to 2.53± 0.85 ($p<0.0001$) after operation. Only 6 cases we could measure CFR of LAD one year after CABG. It was significantly increased from 1.35 ± 0.47:befor CABG to 2.01±0.50:afterCABG and 2.50±0.96:one year after CABG.Conclusions: LITA graft significantly improved coronary flow reserve and may recover myocardial viability in early time after CABG. CFR measurement is useful to evaluate the efficacy of CABG except angiography.
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P502 ^{123}I-MIBG SPECT scintigraphic evidence of cardiac denervation after transmyocardial laser revascularisation

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Transmyocardial laser revascularisation (TMLR) is an invasive therapy used to treat patients with severe refractory angina pectoris in whom standard reatment is insufficient or not possible. Randomised trials have reported a clear clinical benefit (relief of angina and improvement of QOL) of CO2 or Holmium:YAG TMLR compared to maximal medical treatment. Furthermore, initial results of a prospective randomised trial performed by our group also show a reduction in angina and improvement of quality of life (QOL) after XeCl excimer TMLR. The aim of the study described here was to investigate cardiac denervation as a working mechanism of stand-alone TMLR using 123-I-MIBG SPECT scintigraphy (MIBG and noradrenalin have similar molecular structures and both utilise the same uptake and storage mechanisms in sympathetic nerve endings) in combination with an algorithm for quantification of SPECT (Germano et al., J Nuclear Med 2000;41:712-9).
In 8 patients, TMLR was performed using a Ho:YAG (n=3) or XeCl excimer laser (n=5). In all patients angina was reduced by at least 2 classes (classification of the NYHA) at 3 to 12 months follow up, QOL was significantly improved and 123-I-MIBG SPECT scintigraphy showed decreased uptake up to 16 months follow up, indicating sympathetic myocardial denervation after TMLR ($P=0.00002$). Average summed defect scores were 13.4±3.9 pre-operative vs. 23.9±4.3 post-operatively. Pre- and post operative myocardial perfusion scintigraphy did not differ significantly. Our results indicate that relief of angina may be explained by destruction of nociceptors or cardiac neural pathways, resulting in a change in the perception of anginal pain after TMLR.

P503 Coronary artery bypass surgery and risk of sudden death in patients with ischaemic heart disease

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Patients with ischemic heart disease remain at constant risk of sudden cardiac death (SCD). SCD accounts for approximately 50% of all death from cardiovascular causes. The aim of this study was to analyze the influence of surgical coronary artery revascularization on the incidence of SCD in patients without a history of previous CABG who were included in the Bezafibrate Infarction Prevention (BIP) Study (n=2535). During a 7-9 year follow-up period, 541 (21.3%) patients (pts) underwent CABG (mean time from inclusion in study to operation – 2.6 years). Mean age was similar in both groups (CABG + gr. ~59.6 years vs. CABG – gr. ~60.0 years). Patients referred to surgical revascularization included more men (CABG +gr. ~93.3% vs. CABG – gr. ~89.8%) and had a higher prevalence of angina pectoris, heart failure and diabetes (71.5% vs. 57.1%; 32.1% vs. 23.8%; 12.2% vs. 8.4%, respectively). Counterparts without CABG included a higher percentage of smokers (CABG – gr. ~14.4% vs. CABG + gr. ~10.5%), had a higher rate of previous myocardial infarction (81.0% vs. 77.4%, respectively), and received medical therapy with beta-blockers, nitrates and calcium antagonists more frequently (45.3% vs. 38.1%; 66.4% vs. 54.9%; 60.4% vs. 55.7%, respectively). The total cardiac mortality (5.5%) and incidence of SCD (2.4%) among patients who had undergone surgery were significantly lower than in patients without surgical revascularization (10.7% and 6.1%, respectively). After adjustment for different baseline characteristics including the timing of surgery performance, CABG was associated with a 33% reduction in the risk of any cardiac death (RR= 0.67; 95% CI 0.44-1.01) and a 42% reduction in the risk of SCD (RR= 0.58; 95% CI 0.32-1.04).In the group of patients who underwent CABG, an age-dependent increase in death rate from SCD was not observed.
Conclusion: In patients with ischemic heart disease, surgical revascularization was associated with reduction in mortality from SCD.

EXERCISE TESTING/MICELLANEOUS TOPICS

P504 QRS width prolongation precedes ST-segment depression on exercise electrocardiogram in patients with inducible ischaemia

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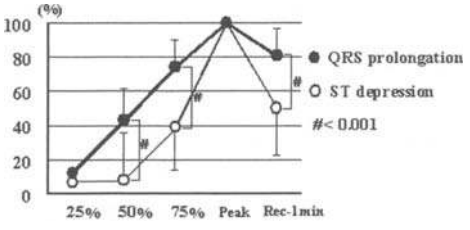
It is well known that exercise-induced ST depression (STD), representing repolarization abnormality, manifests after cardiac workload exceeds an ischemic threshold, and then advances progressively. We, however, have little information about such a time-course of exercise-induced QRS prolongation (QRS-P) representing depolarization abnormality caused by inducible ischemia. This study addressed this issue.
Methods: We examined 31 patients with documented coronary artery disease who had exercise-induced significant STD and visually identifiable QRS-P in treadmill-electrocardiogram (ECG; 25mm/sec). Using digitized 12-lead ECGs (500Hz), we serially measured QRS width and STD at 25, 50, 75, and 100% of total exercise time.
Results: The magnitudes of STD and QRS-P at peak exercise were -4 ± 1 mm and 13 ± 5 msec, respectively. STD did not increase until at 75% of total exercise time, while QRS-P was identifiable at 50%. At 75%, %change to total was 74 ± 16% in QRS-P, but only 39 ± 28% in STD ($p<0.001$).



Time-course of QRS-P and STD.

Conclusion: In patients with inducible ischemia, the time-courses of depolarization (QRS prolongation) and repolarization (ST depression) abnormality in response to exercise differed from each other. QRS prolongation precedes ST depression, possibly serving as an early sign for inducible ischemia without necessitating maximal efforts.

P505 Complex ventricular arrhythmias and myocardial ischaemia during exercise testing in master athletes: prevalence, correlates and outcome

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Between January 1993 and September 2001, 658 consecutive, apparently healthy, asymptomatic, male, competitive athletes (mean age of 57±6 years) underwent a preparticipation cardiovascular evaluation, which included: history, physical examination, 12-lead ECG and maximal ECG exercise testing (cycle ergometer).
During exercise testing, 21 subjects (3,1%) had one or more episodes on non-sustained ventricular tachycardia (NSVT), 14 subject (2,1%) showed asymptomatic ECG abnormalities consistent with myocardial ischemia (MI; horizontal or downsloping ST segment depression >0,1 mV for >80 msec) and 7 subjects (1,0%) showed both episodes of NSVT and MI. All subjects showing NSVT, MI or both during exercise testing were temporarily disqualified from participation in competitive sports and referred for coronary angiography. This diagnostic procedure was performed in 35 of 42 subjects (83,3%), while 7 subjects refused to undergo the procedure and received permanent disqualification (5 with NSVT and 3 with MI). Coronary angiography revealed the presence of significant coronary artery disease (CAD; >50% luminal diameter narrowing in one or more coronary vessels) in 24 of 35 subjects (74,2%). In particular, 7 of 16 subjects with NSVT (43,7%), 10 of 11 subjects with MI (90,9%) and all subjects with both NSVT and MI (100%) showed significant CAD. During follow-up (mean duration 62 months), no major adverse events were noted in athletes who had a negative exercise testing at the initial preparticipation screening. One of the athletes with MI who refused coronary angiography died suddenly while jogging 10 months after disqualification. Necropsy findings were consistent with an acute myocardial infarction in the presence of triple vessel coronary artery disease. Fifteen of 24 subjects with angiographic evidence of CAD underwent myocardial revascularization (11 PTCA and 4 by-pass surgery).
Preparticipation cardiovascular evaluation of male master competitive athletes has a high negative predictive value for subsequent adverse cardiac events. Abnormal findings during exercise testing in such subjects deserve further clinical and laboratory assessment.

P506 Independent association of heart rate response to exercise with cardiac events. An exercise echocardiographic study of 3221 patients

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Objectives: To study the association between heart rate response to exercise and the risk of cardiac death and myocardial infarction after adjustment to the severity of left ventricular dysfunction and the extent of exercise induced myocardial ischemia.
Methods: We studied 3221 patients (age 59 ± 12 years, 1701 men) with known or suspected coronary artery disease, who underwent treadmill exercise echocardiography. Chronotropic incompetence was defined as inability to achieve 85% of the maximal predicted heart rate or a low (<0.8) chronotropic index. The independent association between heart rate response to exercise and endpoints (cardiac death and myocardial infarction) was evaluated by an adjusted risk model, which takes into account clinical parameters, resting ejection fraction and both the presence and severity of ischemia (exercise induced wall motion abnormalities).
Results: The target heart rate was not achieved in 495 (15%) patients. A low chronotropic index was observed in 793 (25%) patients. There were 41 cardiac deaths during a median follow up of 3.2 years. Myocardial infarction occurred in 65 patients. After adjustment for clinical, exercise stress and echocardiographic data, a lower chronotropic index was associated with an increased risk of cardiac death (adjusted risk [AR] 0.65 [CI 0.49-0.85], p = 0.002) and myocardial infarction (AR 0.73 [CI 0.59-0.92], p = 0.007). Failure to achieve 85% of the maximal heart rate was independently associated with increased risk of cardiac death (AR 0.47 (0.24-0.91, p = 0.03).
Conclusion: Impaired chronotropic response to exercise is associated with an increased risk of cardiac death and myocardial infarction even after adjusting for resting ejection fraction and the severity of exercise-induced myocardial ischemia.

P507 Peak VO_2 is more potent than brain natriuretic peptide (BNP) as a prognostic parameter in cardiac patients

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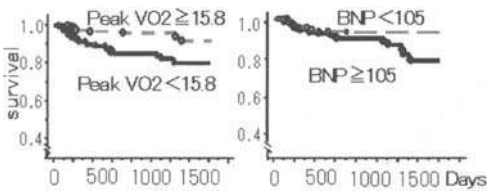
Background: It is known that BNP and peak VO2 are not only indices for severity but also independent predictors of mortality in patients with heart failure, however, there were no data compared the power of these parameters in terms of predictor for survival.
Purpose: We investigated the prognostic significance of BNP and peak VO2 in cardiac patients prospectively.
Methods: Three hundred and ten consecutive patients (male:246, female:64, age:62±37 years) with cardiac disease entered the study. They performed cardiopulmonary exercise tests with a cycle ergometer to determine peak VO2. BNP was measured just before the exercise test.
Results: During 704±422 days of follow-up period, 32 patients died of any causes and 9 were unknown. Peak VO2 was higher in survivors than nonsurvivors (18.5±4.7 vs 13.5±3.7 ml/min/kg, p<0.0001). BNP was lower in survivors than nonsurvivors (112±1537 vs 326±445 pg/ml, p<0.0001) In the univariate Cox proportional hazards analysis, both of peak VO2 and BNP were found to be significant prognostic indices for survival. The multivariate analysis revealed peak VO2 as an independent predictor for all cases mortality (Chi-square:23.9, p<0.0001) and BNP as a significant but slightly weaker predictor (Chi-square:8.6, p<0.005). The Kaplan-Meier curves for the groups categorized by the median values of peak VO2 and BNP were shown in the figure.



Kaplan-Meier Curves for peak VO2 & BNP.

Conclusion: These results indicated that BNP and peak VO2 are independent predictors for survival, while peak VO2 is a more potent parameter than BNP for assessing the mortality in patients with cardiac disease.

P508 Physical fitness does not protect from the prothrombotic effects of acute dynamic exercise in a middle aged population

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Acute dynamic exercise stimulates coagulation, fibrinolysis and thrombocytosis.However the benefits of physical fitness on the balance of haemostasis is controversial.This study aimed to assess the haemostatic changes with exercise in a group of trained subjects in the age group at risk of acute coronary events. Methods: 21 soccer referees peformed a ramp protocol exercise test. Blood sampling was performed pre, immediately post and 30 mins post exercise. Samples were analysed for platelet count, Prothrombin time(PT), Activated Partial Thromboplastin Time(APTT), Fibrinogen, Tissue Plasminogen Activator(tPA). Flow cytometry using CD62(p-selectin) and antifibrinogen antibodies was used to assess platelet activation at rest and in response to ADP, collagen and epinephrine. Results: Expressed as mean(SEM).Statistical analysis was performed using paired t-tests. The mean age of participants was 39.2(5.1)years. Total platelet count increased immediately post exercise (228.2(40.5),278.6 (48.9), p=0.001) remaining elevated at 30 minutes. APTT was reduced immediately post exercise (32.15(3.1),29.7(3.94)p=0.001) with further reduction seen at 30 minutes (32.15(3.1),28.4(3.31),p=0.001). %CD62 expression increased post exercise (0.688(0.52),1.42(1.3)p=0.008) with no significant difference seen at 30 minutes.%Anti-fibrinogen expression increased post exercise (5.19(4.31), 13.01(14.24)p=0.017) with a further increase seen at 30 minutes (5.19 (4.31), 20.47(26.8) p=0.02). Significant increases were seen post exercise in response to epinephrine. tPA increased immediately post exercise (0.47(0.85),6.28(4.45)p=0.001) returning to baseline by 30 minutes. Conclusion: Despite the protective effects of fibrinolysis, the changes in coagulation and platelet activation persist at 30 minutes when tPA has returned to baseline levels. In contrast to previous studies in young athletes, this suggests that in an older population, physical fitness does not protect against the prothrombotic effects of acute dynamic exercise and that the potential risks persist well into the recovery period. Further research should be carried out in an ischaemic heart disease population as haemostatic markers may further improve risk stratification with exercise testing.

P509 Cardiac troponin I (cTnI) and exercise test: correlation with myocardial ischaemia

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The aim of this study was to assess the variation in cTnI, mass CPK MB and CPK activity during an exercise test and to compare these results with thallium 201 tomoscintigraphy.

Methods: 161 subjects (76% male, 63 ± 10 years) with initial (H0) cTnI of <0.4ng/ml were studied.

Blood samples were withdrawn 15 minutes before the exercise test (H0) and 4 hours after (H4). All subjects underwent myocardial tomoscintigraphy after cycle ergometer testing (15 derivations with CM5, CC5 and ML) with an increase in workload every 3 minutes to maximal exercise test and with redistribution imaging at H4.

For the exercise test myocardial tomoscintigraphy, subjects were divided in five groups:

– ischaemic group (77 subjects): without previous acute myocardial infarction (AMI) (28 subjects), with jeopardized myocardium in the territory of AMI (32 subjects) or in a remote territory (17 subjects).

– non ischaemic group (84 subjects): with normal tomoscintigraphy (46 subjects) or previous AMI without ischaemia (38 subjects).

Results: cTnI increased significantly after exercise ($p<0.0001$, Wilcoxon rank test). The means of the ischaemic and non ischaemic groups were compared using the Mann-Whitney U test (table below).

Differences between the five groups were determined by ANOVA for cTnI.H4 ($p=0.005$) and cTnI.H4-H0 ($p=0.021$).

Multiple comparison of means by the Scheffe F test showed that only subjects without previous AMI but with exercise myocardial ischaemia, and normal subjects, differed for these variables ($p=0.0053$ and $p=0.0223$ respectively).

Quantification of the ischaemic myocardial by scintigraphic scores did not show any correlation with the cTnI rates or their variations.

The other markers tested did not show statistically significant variations.

Unit: ng/ml	cTnIc.H0	cTnIc.H4	cTnIc.H4-H0
Ischaemic group (77 subjects)	0.051	0.107	0.056
Non ischaemic group (84 subjects)	0.034	0.063	0.029
p	0.1802	0.0123	0.0252

Conclusion: cTnI showed a statistically significant increase, dependent on exercise, particularly in the ischaemic group, but there was no correlation with tomoscintigraphic extent of exercise ischaemia. In the absence of AMI, the difference in the increase in cTnI between ischaemic and non ischaemic groups was significant, which was not the case in presence of AMI.

P510 Modelling left ventricular dysfunction in the community setting

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Background: With the increasing prevalence of heart failure, community-based programmes to screen for and treat left ventricular systolic dysfunction (LVD) have recently been advocated. However, who best to screen has not been fully elucidated. This study was undertaken to assess this further.

Methods: 1403 subjects ≥45 years old were chosen at random from 7 representative local general practices and invited to undergo a symptom questionnaire, clinical examination, ECG, echocardiogram, urinalysis, spirometry and fasting plasma glucose, N-terminal proBNP (NTP) and lipid profiles.

Results: 732 subjects (52%) attended, 516 (70%) Caucasian and 216 (30%) from ethnic minorities, the majority S. Asian. An ejection fraction was calculable by echocardiography using Simpson's apical biplane method in 703 cases (96%). 38 subjects (5.4%) (3.8-7.2%) were found to have LVD. Multivariate predictors of LVD included prior myocardial infarction, diabetes, a history of heavy alcohol usage, male sex, an abnormal ECG and plasma NTP levels. A multivariate model to predict LVD using these factors was developed. This model gave an area under the ROC curve of 0.95 for predicting significant LVD (left ventricular ejection fraction <45%). A risk-score above 2.83 gave a sensitivity of 92% and specificity of 89% for predicting significant LVD, requiring only 14% of the population to be screened with a one-in-four pick up rate.

Conclusion: Thus simple clinical and biochemical markers of LVD can be combined to create a model that successfully predicts left ventricular systolic dysfunction in the community setting, potentially allowing cost-effective echocardiographic screening, with 86% of the population not requiring echocardiography.

P511 Lean tissue-adjusted versus body weight-adjusted peak oxygen consumption and mortality prediction in chronic heart failure

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Background: peak oxygen consumption (peak VO2) is an important prognostic marker in chronic heart failure (CHF) patients. Peak VO2 reflects oxygen extraction from the metabolically active tissues (i.e., the skeletal muscles); nevertheless, peak VO2 is expressed in mL/min/kg of body weight (peak VO2-weight). We assessed, whether the adjustment of peak VO2 for lean tissue (peak VO2-lean) might provide better prognostic information than peak VO2–weight in CHF patients. Methods and Results: Prospectively, 272 CHF outpatients in stable clinical conditions (mean age 61±12 years, NYHA class 2.3±0.8) underwent a symptom-limited cardiopulmonary exercise testing, and evaluation of body composition with dual-energy X-ray absorptiometry (DEXA). Peak VO2-weight averaged 17.6±5.7 mL/kg/min and peak VO2-lean 25.6±8.1 mL//kg/min. During follow-up (mean 878±777 days), 60 patients died (12-month survival: 89% [95% CI 85-93]). Cox proportional hazard analyses showed that peak VO2-weight and peak VO2-lean predicted survival (both $p<0.0001$), but at the log-likelihood ratio test peak VO2-lean was significantly stronger than peak VO2-weight in predicting survival ($p=0.002$). The receiver operating characteristic area under the curve for peak VO2-lean was significantly greater than for peak VO2-weight at 12, 15, 18 and 21 months follow-up (all $p<0.03$). In patients with mild CHF (NYHA class I and II), peak VO2-lean significantly predicted outcome ($p=0.03$), while peak VO2-weight lost its prognostic power. Conclusions: Adjustment of peak VO2 for lean tissue instead for body weight provides a stronger prognostic parameter. This correction might be particularly useful in mild CHF and in subgroups of patients, such as in women and obese patients, in whom the prognostic value of peak VO2 is less obvious.

P512 Contribution of alveolar and serial dead space to the hyperpnoea of exercise in chronic heart failure

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An increased ventilatory response to exercise is an important feature of chronic heart failure (CHF) and relates to poor prognosis. Increased physiological dead space and low arterial pCO_2 are causative mechanisms. Physiological dead space consists of alveolar and anatomical dead space. Whether the increase in physiological dead space results from an increase in alveolar or anatomical dead space has not been directly investigated yet.

We performed cardiopulmonary exercise testing in 26 patients with CHF (age: 66±11, LVEF: 31±13%, peakVO2: 16±4mL/kg/min, VE/VCO2-slope: 35±7). At rest and during each stage of the test arterial pCO_2 was measured and physiological dead space was calculated. Anatomical dead space was measured by a modified Fowler technique. Consecutively, alveolar dead space and the dead space to tidal volume ratios were calculated.

Of the resting parameters only the anatomical dead space to tidal volume ratio correlated with the VE/VCO2-slope ($r=0.4$, $p<0.05$). At peak exercise, the physiological dead space to tidal volume ratio ($r=0.66$, $p<0.001$), alveolar dead space to tidal volume ratio ($r=0.55$, $p<0.01$), anatomical dead space to tidal volume ratio ($r=0.4$, $p<0.05$) and arterial pCO_2 ($r=-0.58$, $p<0.01$) correlated with VE/VCO2-slope.

On multivariate regression analysis the alveolar dead space to tidal volume ratio ($p=0.01$) but not the anatomical dead space to tidal volume ratio ($p=0.14$) was independently related to VE/VCO2-slope. Alveolar dead space to tidal volume ratio and anatomical dead space to tidal volume ratio were not correlated with each other ($r=0.1$, $p=0.96$).

Our findings confirm that the VE/VCO2-slope is dependent on the physiological dead space to tidal volume ratio during exercise. The increase of the physiological dead space is caused by both an increase in alveolar and anatomical dead space. However, alveolar dead space seems to be more important for VE/VCO2-slope. This suggests a role for an abnormal pulmonary perfusion in the development of exercise hyperpnoea in CHF.

P513 Can natriuretic peptides screen for left ventricular diastolic dysfunction in the community?

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Background: Natriuretic peptides (NPs) have recently been shown to accurately predict left ventricular systolic dysfunction (LVSD) in the community. However, controversy exists as to their ability to predict left ventricular diastolic dysfunction (LVDD) in the absence of LVSD, which may occur in up to half of all heart failure cases. We assessed this further for N-terminal atrial natriuretic peptide (NTA), and N-terminal pro-brain natriuretic peptide (NTB), a newly detectable NP.
Methods: Accordingly, 1403 subjects ≥ 45 years old were chosen at random from 7 representative local general practices and invited to undergo a symptom questionnaire, echocardiography and venesection for plasma NTA and NTB assays. Echocardiographic measures of diastolic dysfunction included mitral inflow peak E and A wave velocities, E/A ratio and E wave deceleration time (DT), isovolumic relaxation time (IVRT) and left atrial diameter (LA).
Results: 732 subjects (52%) attended. Significant correlation was seen between plasma NTB levels and A, E/A, IVRT and LA and between plasma NTA levels and LA only. 187 subjects (26%) had symptoms of dyspnoea. 47 subjects had symptomatic LVDD with either impaired relaxation or restrictive filling patterns on echocardiography, dyspnoea and normal systolic function. Mean plasma levels for those with vs those without symptomatic LVDD but no LVSD were 77.4 and 32.2 pmol/l for NTB ($p<0.0001$) and 2170 and 1760 fmol/ml for NTA ($p=0.001$), respectively. Areas under the ROC curves for NTB and NTA to predict symptomatic diastolic dysfunction were 0.76 and 0.65, respectively ($p=0.04$).
Conclusion: Thus although both NTA and NTB predict LVDD in the absence of LVSD in the community, NTB is a more discriminatory marker, with a greater potential role in screening for LVDD.

P514 Contribution of ergoreflex to respiratory control in chronic heart failure – the reproducibility and the clinical implications of the method

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The overactivation of ergoreceptors (afferents sensitive to metabolic products of skeletal muscle work) is presumed to contribute to the enhanced ventilation and exercise intolerance in patients with chronic heart failure (CHF). The relationships between the ergoreflex activity (the ventilatory response to exercise) and the clinical state of CHF patients have not been comprehensively established, moreover the reproducibility of the applied method has not been tested yet.
Material and Methods: The ergoreflex activity was measured in 53 men with CHF (63.5±12.5 years, NYHA class I/II/III/IV - 8/27/16/2 subjects, EF = 30.5±6.6%) and compared with 17 healthy age-matched men (60.9±11 years, EF = 58.1±4.5%). All subjects underwent maximal cardiopulmonart exercise testing to assess peak oxygen uptake (peak VO2) and ventilatory response to exercise VE/VCO2 slope).
The ergoreflex activity was assessed by 2 runs the 5-minute dynamic handgrip, one run followed by the 3-minute post-handgrip regional circulatory occlusion (PH-RCO), with the continuous measurement of ventilation [l/min-1]. The contributions made specifically by ergoreflex to ventilatory responses were estimated by calculating the differences of ventilation between PH-RCO and the recovery period without PH-RCO (during 1 and 2 minute - ERGO 1-2, during 2 and 3 minute - ERGO 2-3). We also compared the reproducibility of the method in the group of 13 men with CHF.
Results: The advanced clinical state of CHF patients was related to augmented ergoreflex activity: ERGO 1-2 for controls vs NYHA I vs NYHA II vs NYHA III/IV were 0.72 vs 1.82 vs 2.03 vs 4.05 l/min-1, respectively ($F=18.74$, $p<0.0001$). ERGO 2-3 for controls vs NYHA I vs NYHA II vs NYHA III/IV were 0.08 vs 1.08 vs 1.51 vs 3.21 l/min-1, respectively ($F=20.67$, $p<0.0001$). Among CHF patients the significant correlations between ERGO and NYHA class were revealed ($r=0.53$, $p<0.0001$ for ERGO 1-2; $r=0.55$, $p<0.0001$ for ERGO 2-3). CHF patients when compared to controls revealed lower peak VO2 (16.23±4.32 l/kg/min; $p<0.0001$) and higher VE/VCO2 slope (40.98±12.61; $p<0.001$). Variability coefficients for ERGO 1-2 and ERGO 2-3 were 36.1% and 21.5%, respectively.
Conclusions: Our results confirmed that the ergoreflex activity constituted a significant factor discriminating CHF patients and the ergoreceptors overactivation was related to the deterioration of clinical state of CHF patients. The applied method for assessing ergoreflex activity appeared to be moderately reproducible with VC ranging from 21.5% to 36.1%.

P515 Is there any difference in long-term left ventricular pacing compared to biventricular pacing in patients with severe congestive heart failure?

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Cardiac resynchronisation therapy (RT) is a therapeutic option in patients (PTS) with severe systolic heart failure (HF) and conduction abnormalities. According to the PATH I data, left ventricular (LV) stimulation resulted in similar improvement as biventricular pacing during acute hemodynamic testing in PTS with advanced HF and left bundle branch block (LBBB). Potential differences between permanent LV versus biventricular (BiV) stimulation during long-term follow up are not well studied yet.
Until mid 2001 we treated 149 consecutive PTS with severe HF, LBBB and sinus rhythm with RT. Pacing configuration was tailored according to the preimplant hemodynamic testing, which has been described earlier. Baseline characteristics of LV- and BiV-stimulated PTS were comparable. During follow-up 4 PTS died (2 LV, 2 BiV) and 4 were transplanted successfully due to worsening heart failure (1 LV, 3 BiV). All parameters characteristic of HF improved significantly during 6 and 12 months follow-up (FU) (see table below). No significant differences were observed between the LV- and BiV-stimulated groups.
Conclusion: In contrast to published data in this patient cohort the pacing site was chosen according to a preoperative hemodynamic testing. No difference in improvement of clinical and echocardiographic parameters was observed up to 12 month of follow-up.

Abstract P515 – Table

Parameter	Baseline LV	Baseline BiV	LV 6 mo	BiV 6 mo	LV 12 mo	BiV 12mo
n	46	103	35	81	23	51
CAD/DCM/other	18/26/2	29/59/5	13/20/2	27/49/5	16/7	35/14/2
NYHA	3.0 ± 0.4	3.1 ± 0.3	2.0 ± 0.5*	2.2 ± 0.6*	2.0 ± 0.6*	2.1 ± 0.7*
VO2max (ml/kgbw/min)	12.4 ± 2.7	13.4 ± 2.9	15.7 ± 4.0*	15.8 ± 3.8*	15.1 ± 3.4*	16.3 ± 3.2*
VO2AT (ml/kgbw/min)	10.4 ± 2.6	11.0 ± 2.5	12.5 ± 3.3*	13.9 ± 7.0*	12.1 ± 3.0*	13.0 ± 2.0*
Workload (watt)	56.4 ± 23.1	56.1 ± 17.1	75.4 ± 22.2*	72.4 ± 21.6*	77.9 ± 21.9*	75.1 ± 22.3*
6-min walk (m)	296 ± 79	312.2 ± 98.2	414.3 ± 140.2*	407 ± 86.8*	376.3 ± 113.2*	414.5 ± 80.6*
QOL	42.8 ± 16.7	51.6 ± 52.8	25.5 ± 21.6*	23.8 ± 16.1*	19.1 ± 21.9*	27.8 ± 17.7*
LVEDD (mm)	81.3 ± 9	82.1 ± 11.3	76.7 ± 10.4*	72.4 ± 15.1*	77.8 ± 14.5*	73.9 ± 16.3*
QRS (ms)	191 ± 25	186 ± 24				
PQ (ms)	219 ± 43	217 ± 42				
LVEF (%-Echo)	22 ± 7	22 ± 7				

*$p<0.05$ compared to baseline values

P516 The use of brain natriuretic peptide in the diagnosis of heart failure in the community: a randomised, controlled, effectiveness study

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Background: Patients commonly present to general practitioners (GPs) with symptoms of suspected heart failure (HF). However, diagnosis is often difficult in the community setting. Brain natriuretic peptide (BNP) has been shown to be an accurate diagnostic tool in patients with dyspnoea presenting to hospital, but the diagnostic utility of BNP when used by GPs in a community setting is uncertain.
Methods: The study included patients presenting to their GP with symptoms of dyspnoea and/or oedema. Each patient underwent full clinical assessment including ECG, chest radiograph, echocardiography and N-terminal BNP measurement, by an independent study investigator. Patients were randomised as to whether their referring GP received their BNP result (BNP group) or not (control group). All patients were subsequently reviewed by their referring GP who made a diagnosis of HF or not based on clinical grounds alone or with the addition of the BNP. The gold standard diagnosis of HF was the decision of an independent expert panel using ESC criteria. A correct diagnosis was one that agreed with the expert panel, and included correct diagnoses of HF and not HF.
Results: 304 patients were included, mean age 72 yrs (SD 11.4), 65% female; 80% Caucasian; 148 (49%) presented with dyspnoea only, 36 (12%) with oedema only and 119 (39%) with both symptoms. 77 patients (25%) met the case definition for HF; these patients had a significantly higher N-terminal BNP, 286 (SD 319) vs 61 (SD 67) pmol/l, p=0.0001. The percentage agreement of each GP's final diagnosis with the panel diagnosis is shown in the table.The diagnostic accuracy in the BNP group improved 20% compared with 6% in the control group, p=0.002.

Agreement of GP and panel diagnoses

	Control group (no BNP)	BNP group	
Initial GP diagnosis	52%	49%	
Final GP diagnosis (with BNP or clinical review alone)	59%	70%	
Absolute change in accuracy of GP diagnosis	+7%	+21%	p=0.002

Conclusions: In the first prospective, randomised controlled effectiveness trial based in the community, BNP improved diagnostic accuracy of HF by general practitioners. This study supports the availability of N-terminal BNP for the evaluation of patients with symptoms suggestive of heart failure in the community.

P517 Effect of carvedilol on myocardial ischaemia, hibernation and viability in patients with left ventricular systolic dysfunction due to CAD

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Background: Both the myocardial substrate and the ventricular ejection fraction response to beta-blockers are heterogeneous in patients with heart failure and left ventricular systolic dysfunction (LVSD) secondary to coronary artery disease (CAD). The two may be related.
Aims: To determine whether the increase in left ventricular ejection fraction (LVEF) in response to carvedilol amongst patients with heart failure and LVSD secondary to CAD reflects the volume of myocardium affected by hibernation and/or ischaemia.
Methods: An international, multi-centre, double-blind, randomised, parallel-group study was conducted. Patients with systolic dysfunction were initially identified using echocardiography (wall motion index $\leq$ 1.3 (9 segment model), corresponding to a LVEF $\leq$ 39%). In eligible patients, LVEF (radionuclide ventriculography) and myocardial perfusion (MP) (nitrate-enhanced sestamibi at rest and after exertion) were further assessed and reported in a blinded fashion in a core laboratory. Hibernation was defined as an impaired regional echocardiographic wall motion at rest with preserved MP; myocardial ischaemia was defined as a stress-induced MP defect in a segment that had preserved myocardial perfusion at rest. Patients were randomised to placebo or carvedilol (titrated to a target dose of 25 mg bid or 50 mg bid if >85 kg) and then followed for 4 months on maintenance doses (Total duration of treatment about 6 months).
Results: 305 patients were included in the intention to treat analysis. 90% were men, mean age was 62 years, 63% were angina-free during daily activity and 23% were diabetic. 61% were in NYHA class II and 27% in class III. Mean baseline LVEF was 30+11% (SD). 181 (59%) were classified as hibernators. LVEF was unchanged after 6 months on placebo in patients with or without hibernation but rose by 3.3% ($P < 0.0001$) (placebo-subtracted) with carvedilol overall. However, in patients without evidence of viable or ischaemic myocardium carvedilol did not increase ejection fraction, whereas it rose by >5% in patients with 4 or more affected segments.
Conclusions: These data suggest that the effect of carvedilol on LVEF may be mediated by resuscitation of hibernating myocardium and protection from myocardial ischaemia. Medical therapy may be an important adjunct or alternative to revascularisation for these patients. Patients without myocardial ischaemia or hibernation may benefit from beta-blockers by mechanisms other than an improvement in LVEF.

P518 Interleukin-6 and tumor necrosis factor-a levels increase in response to maximal exercise in patients with chronic heart failure

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Background: Chronic heart failure (CHF) is characterized by the activation of neurohormones and cytokines. Strenuous exercise causes activation of both systems, but the effect of exercise on cytokine is not known in patients with CHF. This study determined whether maximal exercise induces activation of cytokines in patients with CHF.
Methods: Plasma interleukin-6 (IL-6), tumor necrosis factor (TNF)-a, epinephrine, norepinephrine, and atrial & brain natriuretic peptide (ANP & BNP) were determined before and after symptom-limited cardiopulmonary exercise testing in 80 patients with CHF (age=58±1 years, LVEF=38±1%, peak VO2=18.8±0.5 ml/min/kg) and age-matched 33 normal controls.
Results: Resting IL-6 (Controls vs CHF: 1.3±0.2 vs 2.4±0.3 pg/ml, $p<0.001$) and TNF-a (2.7±0.2 vs 3.8±0.2 pg/ml, $p<0.01$) were elevated in CHF. IL-6 and TNF-a were positively correlated (r=0.35 and r=0.28, respectively) with plasma norepinephrine, and were negatively correlated (r=-0.28 and r=-0.31, respectively) with peak VO2. Maximal exercise increased IL-6 and TNF-a in controls (by 92% and by 12%, respectively) and in patients with CHF (by 59% and by 13%, respectively) (all $p<0.01$). Changes in IL-6 (delta-IL-6) was correlated with delta-epinephrine (r=0.63, $p<0.0001$) and delta-norepinephrine (r=0.57, p=0.0006) in controls, but not in patients with CHF. Delta-TNF-a was correlated with delta-ANP (r=0.28, p=0.01) only in patients with CHF.
Conclusions: Cytokine activation at rest was associated with high plasma norepinephrine and low exercise capacity. Maximal exercise caused increases in IL-6 and TNF-a concentrations. Sympathetic activation seems to be important for the IL-6 increase during exercise in controls. In patients with CHF, changes in ANP during exercise was associated with the exercise-induced increase in TNF-a, but still unknown mechanisms are involved for the cytokine activation during exercise.

P519 Predictive value tissue Doppler echocardiographic findings on positive left ventricular remodelling induced by cardiac resynchronization therapy

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Background and Introduction: Resynchronization of left ventricular (LV) contraction is considered a mechanism for the clinical benefit observed in heart failure patients (CHF-pts.) with a wide QRS complex treated by cardiac resynchronization (CRT). We analyzed whether mechanical LV asynchrony as assessed by tissue Doppler echocardiography (TDE) and its evolution after CRT is predictive for echocardiographic measures of LV function (LVF) during follow-up.

Methods and results: 49 CHF-pts treated with CRT were studied. Pt. selection for CRT was based on clincal and ECG criteria plus invasive hemodynamic testing. TDE curves of septal and lateral wall segments were obtained 144±94 (30-390) days after CRT, and were superimposed on each other, to allow analysis of timing and direction of movements. Timing was measured in ms (corrected for a cycle length of 1000 ms). Pts. were classified as TDE-responders (TDE-R: asynchrony at baseline, corrected by CRT) vs. non-responders (TDE-NR: either not asynchronous at baseline, or persisting asynchrony despite CRT) and LVF responders (LVF-R: diameter reduction of >10%) vs. nonresponders (LVF-NR). Results are summarized in the table.

Variable	TDE-R (n=29)	TDE-NR (n=20)	p-value
Baseline LV diameter (mm)	79±9	82±11	0.2
LV diameter reduction (mm)	9±11	3±9	0.08
Baseline LV-EF (%)	23±8	20±12	0.2
LV-EF gain (%)	9±10	2±12	<0.05
LV-R (n; %)	19/29 (66%)	5/20 (25%)	<0.01
LV filling time gain (ms)	70±103	30±168	0.3
Baseline QRS width (ms)	191±20	200±26	0.2

Conclusions: The remodeling effect of CRT is largely limited to TDE-R, although TDE-NR also demonstrated some benefit. TDE evaluation should therefore be routinely performed in pts. considered for CRT. Traditional selection criteria including hemodynamic testing do not reliably predict the success of CRT with respect to echo measures of LVF.

P520 Clinical characteristics and prognosis of patients with heart failure and preserved or reduced left ventricular ejection fraction

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Objectives: To determine the clinical and prognostic differences between heart failure patients with preserved and deteriorated systolic function, defined as possession of left ventricular (LV) eiection fractions > 50% and < 50%, respectively.

Patients and Methods: We studied the records of 229 conqestive heart failure (CHF) patients aged 66.7± 11.7 years (95 women, 134 men) who had been admitted to a Cardioloqy Service for CHF in the period 1991-1994, and whose LV systolic function had been echocardio-graphically evaluated within 2 weeks of admission. Data were collected on the main clinical findings, supplementary examinations, treatment, and duration of hospitalization; the patient's situation in the spring of 1999 was evaluated by searching the general archives of the hospital and by telephone survey.

Results: LV systolic function was preserved in 29% of patients. The preserved and deteriorated groups differed significantly as regards the female/male sex ratio (greater in the preserved group), and the presence of third sound, cardiomegaly, alveolar oedema, ischaemic cardiopathy and treatment with angiotensin-converting enzyme inhibitors (all more prevalent in the deteriorated group). There were no statistically significant differences as regards age; NYHA functional class; the presence of sinus rhythm, fibrillation or LV hypertrophy; treatment with drugs other than ACE inhibitors; or survival. In the group as a whole, the survival rates after 3 months and 1 and 5 years were 92.6%, 80% and 48.4%.

Conclusion: In view of the poor prognosis of CHF patients with preserved LV systolic function (currently treated empirically), controlled clinical trials should be carried out to optimize their treatment.

Key words: congestive heart failure. Systolic function. Prognosis,

P521 Response to multisite pacing in ischaemic cardiomyopathy: which site to choose

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Introduction: As multisite pacing is a promising new therapy for heart failure patients in class III and IV, still not a lot of knowledge is available on the optimal pacing site and why some patients do not respond and what kind of patient will not respond

Objective: in temporary multisite pacing we tried to establish how many pts are responders to what pacing combination.

Methods: in 24 pts with ischemic cardiomyopathy with QRS duration over 120 msec and EF below 35% (21 male/3 female, age 71±8 yrs) we used temporary multisite pacing to establish the best position for each patient. We used temporary 6Fr pacing lead V116 and specially prepared PTCA Galeo wires (Biotronik) through an Amplatz L2 guiding catheter to position in RV apex, RV outflow tract, right atrium for VDD pacing and anterior and posterolateral branches of the coronary sinus. We then used Doppler flow over the aortic valve to measure Cardiac Index (CI). A responder was defined as an increase of 10% or more.

Results: At bifocal right postion (RV apex + outflow tract) 10 (59%) pts were nonresponders and 7 (41%) were responders. The delta CI (maximal CI minus baseline CI) was 5.5±2.5 and 16.7±4.1% resp. (p<0.0001). Cs postlat+apex had 8 (47%) nonresponders and 8 (47%) responders with delta cardiac index 4.5±4.9 and 15.6±4.3% resp (p<0.0001). Cs postlat+rvot had 11 (65%) nonresponders and 5 (29%) responders with delta cardiac index 5.6±3.8 and 17.1±8.2% resp (p<0.0002). Cs ant+apex had 9 (53%) nonresponders and 8 (47%) responders with a delta cardiac index of 2.1±5.9 and 15.2±3.1% resp (p<0.0002). Cs ant+rvot had 14 (58%) nonresponders and 6 (35%) responders with a delta cardiac index of 3.6±4.9 and 14.1±3.9% resp (p<0.001).

Conclusion: this study shows clearly that definite LV lead positioning should be individually tailored for each patient. How to determine with easier methods than with this lengthy temporary pacing procedure to know where to be has yet to be determined.

P522 Neurohumoral activation predicts enhanced ventilatory response to exercise in patients with chronic heart failure

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Background: Chronic heart failure (CHF) is characterized by the activation of neurohormones and elevated slope of ventilatory response to exercise (VE/VCO2). Patients with an enhanced VE/VCO2 slope reported to have exercise intolerance, abnormal hemodynamics, augmented chemoreceptor sensitivity, and poor prognosis. However, the relation between the enhanced ventilatory response to exercise and multiple neurohumoral factors has not been studied. This study determined whether neurohumoral activation is a predictor of VE/VCO2 slope in patients with CHF.

Methods: Plasma concentrations of norepinephrine, renin-angiotensin system activity, atrial & brain natriuretic peptide (ANP & BNP), and endothelin-1 were determined in 71 patients with CHF (age=61±1 years, NYHA functional class I/II/III: 24/31/16, left ventricular ejection fraction=35±1%, peak VO2=17.9±0.9 ml/min/kg) and age-matched 25 normal controls. VE/VCO2 slope was calculated by the relation between ventilation and carbon dioxide production at cardiopulmonary exercise testing.

Results: Patients with CHF had significant neurohumoral activations with increased plasma norepinephrine (Controls vs CHF; 201±11 vs 302±28 pg/ml), ANP (23.7±4.3 vs 74.9±8.0 pg/ml), BNP (19.7±3.5 vs 218.2±29.1 pg/ml) and endothelin-1 (2.32±0.12 vs 2.64±0.13 pg/ml) levels compared to normal controls (all p<0.05). VE/VCO2 slope (Controls vs CHF; 27.5±0.6 vs 34.6±0.9, p<0.01) was higher in CHF. At the univariate analysis, age (p<0.01), body weight (p<0.01), NYHA functional class (p<0.0001), plasma norepinephrine (p<0.0001), plasma ANP (p<0.0001), plasma BNP (p<0.0001), and plasma endothelin-1 (p<0.0001) significantly related with VE/VCO2 slope among patients with CHF. Both plasma ANP (r=0.59, p<0.0001) and plasma norepinephrine levels (r=0.55, p<0.0001) had significant positive correlation with VE/VCO2 slope in CHF. Multivariate analysis revealed plasma levels of ANP and norepinephrine predicted VE/VCO2 slope independent of NYHA functional class and body weight (overall R=0.80, p<0.0001).

Conclusions: Plasma ANP and norepinephrine levels are independent predictors of VE/VCO2 slope in patients with CHF. These findings suggest that neurohumoral activation significantly contributes to the enhanced ventilatory response to exercise in patients with CHF.

P523 Effects of carvedilol therapy on exercise tolerance in patients with chronic heart failure

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Background: Recent clinical trials have clearly demonstrated that beta-blockers (BB) prolong survival in chronic heart failure (CHF), but whether BB improve pts exercise tolerance remains controversial. In this study we assessed the effect of 3-month therapy with carvedilol on functional capacity in pts with mild to moderate CHF.

Methods and Results: Among 50 consecutive CHF pts referred to our institution for initiation of BB therapy (carvedilol), 42 pts met the entry criteria (>1 month stability, NYHA class II-III, optimal treatment obligatory with ACE inhibitor) and were included into the study. Carvedilol (3.125mg od) was started and titrated up to a maximal tolerated dose (aim: 25 mg bd). Ten pts did not tolerate carvedilol and were excluded. The remaining 32 Pts (28 men, 62±9 years, NYHA class II/III: 19/13) completed the 3-month study period. At baseline and after 3-month therapy cardiopulmonary exercise testing was performed and the following parameters were analysed (table): total exercise duration (Texer), peak oxygen consumption (peakVO2), ventilatory response to exercise (VE/VCO2 slope), anaerobic threshold (AT), and respiratory quotient (RQ) (mean ± SD, * p<0.05):Baseline(n=32)vs End of the study (n=32): NYHA class (I/II/III) 0/19/13 vs 3/24/5*, Texer (s) 457±140 vs 488±164, Peak VO2 (ml/min/kg) 20.9±5.9 vs 21.4±6.1, VE/VCO2slope 35.4±13.4 vs 32.6±6.1, AT (ml/min/kg) 12.4±4.7 vs 13.9±4.6, RQ 1.08±0.06 vs 1.09±0.04.

In pts treated with carvedilol, subjective improvement in functional capacity as evidenced by NYHA class was not paralleled by objective changes in cardiopulmonary indices. Pts were further divided into 2 groups, based on the presence (n=12) or absence (n=20) of left ventricular restrictive filling pattern (defined as mitral E/A ratio > 1 and deceleration time <120ms) at baseline ECHO-2D recordings. In those with restrictive filling pattern, carvedilol significantly decreased VE/VCO2 slope (41.9±17.2 vs 32.3±10.3, p=0.03) and increased AT (11.8±4.4 vs 14.1±2.4, p=0.06, baseline vs after 3-month therapy, respectively) with concomitant restoration of transmitral flow in 9/12 Pts.

Conclusion: In this study carvedilol therapy exerted neutral effects on objective indices of exercise tolerance in Pts with CHF. Whether in Pts with restrictive LV filling pattern BB may be particularly effective in improving exercise intolerance warrants further investigation.

P524 Tool for prediction of match between positive exercise treadmill test and need for revascularization

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Objectives: Can true positive test be predicted using risk score as tool developed from coefficients using multivariate logistic regression risk-prediction model. Therefore we analyze total of 4268 exercise treadmill tests performed between 01/1999 and 01/2000 using a multivariate logistic regression analysis to identify predictors. The final model vas validated on an independent data set from 836 positive treadmill test results and angiography findings (performed in period from 10/2000 to 09/2001). Match between positive test and need for revascularization assessed by angiography finding was considered as true positive test. A tool for predicting an individual patients risk was developed using a risk prediction score representing the rounded coefficients of the logistic regression model to the closest half-integer.

Results: False positive test occurred in 17.6% of patients. Multivariate regression analysis identified: previous myocardial infarction (odds ratio [OR] 11.5, 95% confidence interval [CI] 9.4-13.8; p<0.001); previous positive test (OR 7.7, 95% CI 5.1-9.2; p<0.001); previous angioplasty (OR 2.7, 95% CI 1.8-3.4; p<0.001); male gender (OR 2.2, 95% CI 1.5-3.4; p<0.001); age 55-60 years (OR 1.8. 95%CI 1.3-2.6; p<0.001) age 61-65 years (OR 2.3, 95% CI 1.6-3.2) over 66 years (OR 2.9, 95% CI 2.1-4.2; p<0.001); exercise below 60% of cardiovascular capacity (OR 2.4, 95% CI 1.3-3.4; p<0.001) Hypotensive response (OR 5.5, 95% CI 3.7-6.3);Symptom limited exercise (OR 3.1, 95% CI 1.6-4.5; p<0.001) as independent predictors of true positive test. Analysis identified Female gender (OR 1.8, 95% CI 1.2-2.2; p<0.001); Hypertensive response to exercise (OR 3.7, 95% CI 2.2-5.2; p<0.001); dispnoe (OR 2.3, 95% CI 1.2-3.2; p<0.001) as independent predictors of false positive test.

Conclusions: We conclude that risk-score tool can facilitate accuracy of positive exercise test.

P525 Patients with coronary stenoses show abnormal regional strain and backscatter despite normal function

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Background: Although structural and functional changes have been reported in hypoperfused myocardium with left ventricular (LV) dysfunction, it is not known whether such changes occur even in hypoperfused myocardium with normal LV function. We sought whether regional myocardial structural and functional abnormalities in coronary artery disease (CAD) patients with normal LV systolic function could be detected using integrated backscatter (IB) and strain rate (SR) imaging.

Methods: Forty-nine CAD pts (defined by ≥50% stenosis) and 18 controls without significant CAD were studied. All pts had normal wall motion (LV ejection fraction; >55%) and no LV hypertrophy (LV mass index; <131 g/m^2 in men and <100 g/m^2 in women). Gray scale and color tissue Doppler imaging from 3 apical views were stored and analyzed off line and all pts underwent coronary angiography within 6 months. Wall thickness at end-diastole (WT) and percent wall thickening (%WT) were measured in each of 12 segments (excluding apical segments) using anatomical M-mode echocardiography. Cyclic variation (CV) of IB was measured in all 16 segments, and peak strain and SR was calculated in each wall. Calibrated IB intensity (CIB), corrected for pericardial IB intensity, was measured in the septum and posterior wall.

Results: Segments (n=470) subtended by significant stenoses were divided according to stenosis seveity into 3 groups; mild (50-69%, n=170), moderate (70-98%, n=230) and severe (≥99%, n=70). Each parameter in each group was compared with that in control segments (n=288) from pts without CAD (Table). Segments with severe stenosis showed significantly lower CV than that in control segments (p<0.05), with no difference in WT or %WT.

Strain and IB parameters vs stenosis

	Control	Mild	Moderate	Severe
CV (dB)	7.6±2.8	7.7±2.8	7.5±2.6	6.7±2.8*
CIB (dB)	-24.9±7.4	-21.9±7.0	-23.9±6.3	-20.7± 5.9
Peak strain (%)	-26.6±5.2	-27.2±4.8	-26.4±5.6	-26.8± 6.7
WT (mm)	8.6±1.1	8.7±1.4	8.6±1.5	8.7±1.2
%WT (%)	44.5±14.0	45.7±14.7	46.1±12.3	43.5±10.6

Conclusions: Regional myocardial function is impaired in segments with severe coronary stenosis, even without overt infarction and with preserved systolic function.

P526 Trans-ulnar coronary interventions: a feasibility study

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Since trans-radial coronary catheterisation is not always possible, we have explored the possibility of using the ulnar artery (UA) as an alternative route for coronary intervention.

Percutaneous trans-ulnar coronary catheterisation has been attempted in 43 patients after positive oxymetry (reverse modified Allen test). Reasons for UA approach was operator preference in 41 cases and failed radial artery puncture (n=2). There were 25 men and 18 women. Mean age was 63±12 years. Mean height was 170±7 cm and mean weight was 81±17 kgs. Body surface area was 1.9 ± 0.2 m^2. In 5 cases, the UA could not be canulated due to spasm. In 1 case of planned left main PTCA, we had to change from left UA to right femoral route due to lack of back-up support. Sheath size was 4Fr (n=1), 5Fr (n=26), 6Fr (n=10), 7Fr (n=1). The right UA was used in 35 cases and left UA in 3 cases. There were 25 diagnostic angios (2 previous CABG) and 13 angios followed by adhoc PTCAs. To canulate the left main, we used Multipurpose (n=20), Judkins left (n=16) or left Amplatz (n=2). To canulate the RCA, we used Multipurpose (n = 20), Judkins (n=16) or left Amplatz (n=2) catheters. For PTCA, left main was canulated with an extra-back up (n=10) catheter and RCA with Barbeau (n=2) or right Judkins (n=1) catheters. Abciximab was used in 4 cases and Eptifibatide in 3 cases. Intravascular ultrasound was performed in 5 cases and brachytherapy in 1 cases. The mean duration of the procedures was 40 ±22 minutes. There was no clinical complication.

Trans-ulnar catheterisation may be an elegant substitute for trans-radial approach in selected cases.

P527 Does nitroglycerin mask a warm-up phenomenon in patients with coronary artery disease?

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The aim of this study was to assess the effects of nitroglycerin on a warm-up phenomenon (i.e. attenuation of myocardial ischemia during repeat exercise testing) in patients with stable angina pectoris.

Methods: Twenty males (52±6 years) with 1-2-vessel coronary artery disease and positive baseline treadmill exercise test (TET) were randomized in a double-blind, 3 day cross-over period study to receive 0,5 mg sublingual nitroglycerin or placebo immediately prior each of two consecutive TET with at 15-minute recovery intervals.

Results: Significantly improvement in some parameters of myocardial ischemia was observed during second TET compared to the first TET after placebo. The duration of exercise was prolonged from 312±160 to 387±165 seconds ($p<0.001$), the maximal ST depression was decreased from 2.1±0.43 to 1.7±0.57 mm ($p=0.003$), as well as the recovery time from 349±106 to 233±86 seconds ($p<0.001$) and the number of ECG leads with 1 mm ST depression from 3.2±1.7 to 2.7±1.6 ($p=0.037$). The heart rate at onset of ischemia increased from 120±18 to 126±21 beats/min ($p=0.001$), the double product at 1,5-mm ST depression increased from 17.54±3.4 to 19.53±4.3 mm Hg/second ($p<0.001$). However, these parameters of two consecutive TET did not change after nitroglycerin administration with a significantly drug test interaction ($p=0.009$, at two-way ANOVA).

Conclusion: Nitroglycerin with 0,5 mg sublingual dose increased anti-ischemic tolerance but it should mask the warm-up phenomenon during repeat exercise tests.

P528 The serum hydroxyproline level, a maker for collagen, is a biochemical marker in patients with vulnerable plaque or plaque disruption

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Background & Objectives: The activated macrophage secretes proteinases that can break down both collagen and elastin to peptides and eventually amino acids.Evidence from several laboratories suggests that collagen breakdown in coronary artery disease is important for identification of vulnerable plaque or disruption. This breakdown of these structural molecules of the extracellular matrix can weaken the fibrous cap, rendering it particularly susceptible to rupture and precipitation of acute coronary syndromes. Hydroxyproline released in the serum used as an evidence of collagen breakdown or synthesis. Our objective was to compare these collagen markers among patients with stable angina, patients with unstable angina or AMI and healthy individuals.

Methods: Venous blood sampling was obtained at the time of admission. We examined the serum levels of hydroxyproline in 15 patients with stable angina, in 15 patients with unstable angina (Braunwald II or III), in 20 patients with AMI and in 10 healthy subjectes. Serum hydroxyproline level was measured by the amino acid analysis system (HPLC: Pico-Tag system, Waters). Serum c-reactive protein (CRP) was measured in same samples.

Results: There was significant difference in serum hydroxyproline level in patients with acute myocardial infarction (4.92±1.89 μg/L), unstable angina (2.92±0.81 μg/L), stable angina (2.22±1.29 μg/L) and normal control group (2.35±0.92 μg/L). There was no significant difference in serum hydroxyproline level between the stable angina and normal control group ($p>0.05$). However, there was significant elevation of serum hydroxyproline in the patients with unstable angina ($p=0.045$) and AMI ($p<0.01$) compared to the patients with stable angina. There was no relationship between serum hydroxyproline and CRP level ($p>0.05$).

Conclusion: Serum hydroxyproline level in the acute coronary syndrome was significant elevation. So, we think that serum hydroxyproline could be a good biochemical for vulnerable plaque in the coronary artery disease.

P529 Plasma interleukin-6 levels are increased in coronary artery ectasia

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Objective: Coronary artery ectasia is a relatively rare abnormality which is considered to be congenital or acquired in origin. Acquried coronary ectasias have been most commonly attributed to atherosclerosis and less frequently to inflamatory diseases. Recent studies have suggested a cytokine-induced tissue inflamation in the pathogenesis of abdominal aortic aneurysms, depending on the demonstration of increased levels of circulating interleukin-6 (IL-6) in these patients. The aim of this study was to investigate whether a similar association also exists for patients with coronary ectasia, which may also be regarded as an abnormal dilatation of the arterial system.

Method: The study group was composed of 43 patients (58±9.4 years, 26 males) with coronary ectasia and the control group consisted 48 consecutive patients (55±11 years, 20 males) with angiographically normal coronary arteries. Coronary diameters were measured as the maximal diameter for each segment by quantitative angiography. A coronary diameter index was defined for each segment as the coronary diameter divided by the body surface area (BSA). In the study group, a coronary segment with a diameter index of more than 1.5 fold of the control group was defined as ectatic. IL-6 levels were measured from the venous blood samples.

Results: There were no significant differences between the two groups with regard to baseline characteristics such as age, sex, BSA, hypertension, diabetes, smoking and lipid profile. Coronary ectasia was present in a single vessel in 28 patients and in two coronary vessels in 12 patients in the study group. Diffuse ectasia in 3 vessels was observed in 3 patients. Serum IL-6 levels were significantly higher in patients with coronary ectasia compared with the control group (5.18±2.04pg/ml vs 4.13±0.5pg/ml,$p=0.002$). The mean serum IL-6 levels in patients with single vessel,two vessel and diffuse ectasia were as follows: 5.37±2.03pg/ml,4.68±2.04pg/ml and 5.57±2.71pg/ml, respectively. There was no significant correlation with the maximal diameter of the most dilated coronary segment and IL-6 levels in patients with coronary ectasia ($r=0.10$,$p=0.50$).

Conclusion: Results of this study have demonstrated increased levels of circulating IL-6 in patients with coronary ectasia which might indicate a possible role of inflamatory process in the pathogenesis of dilated coronaropathy. Absence of a significant correlation between the dimensions of the ectatic segments and IL-6 levels might be due to the narrower range of the diameters of the coronary arteries compared with the abdominal aorta.

P530 Changes in the cytokine levels reflect the that of functional capacity in patient with heart failure

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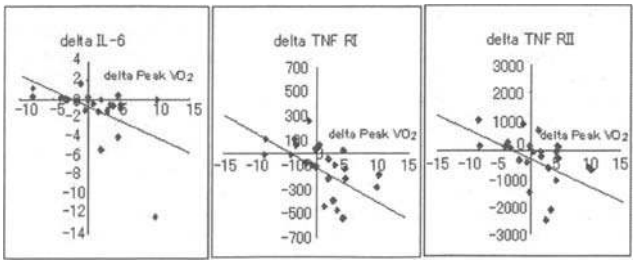
Recently several investigators have reported that pro-inflammatory cytokines such as tumor necrosis factor (TNF) and its receptors are not only indices for severity but also predictors of mortality in patients with heart failure. We investigated the relationship between cytokine revels and peak VO2, which is a conventional parameter for the prognosis, in the time course of medical treatment in heart failure patients.

Methods: Twenty-three patients with stable chronic heart failure (average ejection fraction: 28.9±9.2%, 60.3±10.7 years) who performed cardiopulmonary exercise testing (CPX) using a cycle ergometer with a ramp protocol were enrolled in this study. Nine months after the initial CPX, the second exercise testing was performed. Plasma concentrations of brain natriuretic peptide (BNP), TNF-soluble receptors I and II (TNFR-I and R-II), and interleukin-6 (IL-6) were measured at the same time.

Results: In the initial CPX, peak VO2 was 17.8±6.6 ml/min/kg. Peak VO2 was did not change as an average at the second CPX (18.9±5.6), while 13 patients out of 23 showed an increase in peak VO2 (4.7±2.9). The plasma cytokine levels in the initial test were as follows; IL-6:2.0±3.2 pg/ml, TNFR-I:1046±336 pg/ml, TNFR-II:2545±1193 pg/ml, and BNP:158±120 pg/ml. And they correlated negatively to peak VO2. The change in peak VO2 (the second-the initial) correlated negatively to those of IL-6 ($r=0.52$, $p=0.01$), TNFR-I ($r=0.54$, $p=0.008$), TNFR-II ($r=0.45$, $p=0.03$), and BNP ($r=0.55$, $p=0.01$).



Delta values of cytokine and peak VO2.

Conclusion: The changes of plasma cytokine levels related to that of exercise capacity. This result suggests that cytokine measurements are useful in predicting improvements or deteriorations in functional capacity in ambulatory patients with chronic heart failure.

P531 The relationship between functional impairment and neurohormonal abnormalities

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Peak VO2 is an established parameter for evaluating the severity of heart failure. On the other hand, investigators have recently reported that neurohormonal parameters are useful for the same purpose. This study was designed to evaluate the relationship between peak VO2 and neurohormonal abnormalities.

Methods: We performed cardiopulmonary exercise testing (CPX) in 105 patients with acute myocardial infarction at 1 month after the onset. Plasma concentrations of noradrenaline (NA), brain natriuretic peptide (BNP), and tumor necrosis factor-alpha soluble receptors (TNFR-I and TNFR-II) were measured. Patients were classified into the following three groups: very low capacity (VL: peak VO2<18 ml/min/kg, n=11), low capacity (L: peak VO2=18 to 24 ml/min/kg, n=44), and preserved capacity (P: peak VO2 >24 ml/min/kg, n=50).

Results: Ejection fraction was similar in the three groups. NA was higher in the VL group than in the L group (451±249 vs 341±207pg/ml), and NA was higher in the L group than in the P group(341±207 vs 239±127pg/ml). BNP was also higher in the VL group than in the L group (256±178 vs 85±84pg/ml), and BNP was higher in the L group than in the P group (85±84 vs 49±41pg/ml). While TNFR-I (1257±496 vs 1043±365 pg/ml) and TNFR-II (3566±759 vs 2778±786pg/ml) were higher in the VL group than in the L group, their levels were similar in the L and P groups.

Conclusion: Among heart failure patients, NA and BNP increase even in those with mild exercise intolerance, while TNFR-I and TNFR-II increase in those suffering from more severe cardiac conditions.

P532 Low-frequency components of exercise VO_2 are coupled to VE/VCO_2 slope in patients with heart failure

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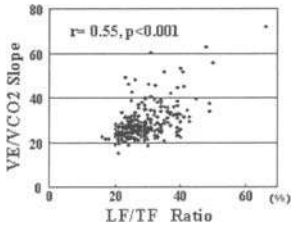
Although elevated VE/VCO2 slope (exercise hyperventilation) measured at exercise testing with respiratory gas analysis (CPX) has been shown to have important pathophysiological and prognostic implications in patients with heart failure, the responsible mechanisms are incompletely understood. Similarly, we have few available data explaining the origin of abnormal slow oscillations in ventilation and VO2 seen in these patients. If the same mechanism such as enhanced CO2 chemosensitivity may operate in the manifestation of these two abnormalities, there should be a close relationship between them. We therefore examined the hypothesis that these two abnormalities are coupled to each other. Since we have no available method for quantifying slow oscillations, we estimated VO2 low-frequency components measured at CPX.

Methods: We performed symptom-limited CPX on bicycle ergometer (ramp protocol) in 184 consecutive patients with mild to severe heart failure due to dilated cardiomyopathy (DCM). By using VO2 data (every 6 sec) from rest to peak exercise, we computed low frequency power (LF) in the range of 0.5-1.25 cycles/min and total power of VO2 (TF) with serially performing FFT (4-min time-window, overlapping every 30 sec). VE/VCO2 slope was measured according to the standard method.

Results: LF/TF ratio was significantly correlated with VE/VCO2 slope (r=0.55, p<0.001) as shown in the figure.



LF/TF Ratio vs. VE/VCO2 slope.

Conclusion: Predominant low-frequency components of VO2 were associated with elevated VE/VCO2 slope, suggesting the possibility that the same mechanism, such as enhanced CO2 chemosensitivity, contributes to the genesis of elevated VE/VCO2 slope and slow oscillations in VO2.

P533 Effect of a home based telecardiology on chronic heart failure outcomes: a case control pilot study

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Chronic heart failure (CHF) remains a common cause of disability and death and the extensive requirement for hospital admission represents a major burden to health-care system. Previous investigations suggest that home-based intervention has the potential to decrease the rate of hospital readmission, prolong event-free and total survival and improve quality of life.

Aim of our study was to analyse a home based intervention with a telecardiology system in CHF patients (pts).

Seventy four CHF pts, aged 59±9 years in stable conditions and with optimised therapy were enrolled. The program consists in a transtelephonic follow-up and ecg monitoring (HBT: home based telecardiology) followed by paramedical and medical team. The pts received a portable device, transferring by a mobile or fixed telephone a one lead trace to a receiving station where a nurse was available for reporting and interactive teleconsultation (providing information on health status, symptoms, weight, diuresis, drug adjustment and optimization). The patient can call the centre when he need (teleassistance), while the team call the patient with scheduled appointment (telemonitoring). Comparison of one-year clinical outcomes were made between HBT patients and a control group of 74 patients matched 2:1 to HBT patients on age, sex, NYHA class, EF% and VO2 peak (UC). A significant reduction in instabilisations (55.4% vs 23.9%; p<0.0001; RRR 0.57; CI 0.12-0.59) and hospitalisations (36.5% vs 18.3%; p<0.01; RRR 0.5; CI 0.18-0.83) and were observed in HBT group in comparison with UC group. No significant difference was found on mortality between groups. These results suggest that a telecardiology service could detect and prevent clinical instabilisations and reduce rehospitalisation in CHF patients.

THE PERIPHERY IN CHRONIC HEART FAILURE

P534 Chemical mediators of the muscle ergoreflex in chronic heart failure: a putative role for prostaglandin in reflex ventilatory control

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Background: The overactivity of ergoreceptors (intra-muscular afferents sensitive to products of skeletal muscle work) may be responsible for the abnormal responses to exercise and symptoms of exercise intolerance in chronic heart failure (CHF); however little is known of the chemical nature of the stimuli involved. We investigated biochemical factors (H^+, PvCO2, PvO2, HCO3, K^+, Phosphate, Lactate, PGE2, PGF1alpha, bradykinin) potentially involved in ergoreceptor activation.

Methods and Results: Sixteen stable CHF patients (64.9±2.7years, peakVO2 15.8±0.7ml/kg/min) and 10 age-matched normals were studied. The ergoreceptor test involved two 5-minute handgrip exercises. On one occasion the subjects recovered normally (control recovery), while on the other a post handgrip regional circulatory occlusion (PH-RCO) was induced in the exercising arm, isolating the stimulation of the ergoreceptor after exercise. The ergoreflex was quantified as the difference in ventilation between the PH-RCO and the control recovery periods. During the protocol the local muscular blood effluent concentrations of metabolic mediators were assessed. Patients had an ergoreflex effect on ventilation greater than normals (4.8±1.4 vs. 0.4±0.1L/min, p<0.01). During the ergoreflex test in patients, the following metabolites were elevated with respect to resting values in comparison with normals: PGE2 (3.7±0.7 vs. 1.1±0.2pg/ml), PGF1alpha (16.2±2.8 vs. 7.2±1.2pg/ml) and bradykinin (2.1±0.3 vs. 1.0±0.1pg/ml), p<0.05 for all comparisons. Only the increases in prostaglandin were predictors of the ergoreflex response (r>0.41, p<0.01). Eight patients on aspirin vs. those eight not on aspirin presented lower ergoreflex activity in the control of the ventilatory response (2.1±0.6 L/min vs. 7.5±2.3 L/min, p<0.05), associated with reduction of blood concentration of PGF1a (10.7±2.9 pg/ml vs. 21.1±3.2 pg/ml, p<0.05) and not significant changes in PGE2 (3.1±0.8 pg/ml vs. 4.6±0.8 pg/ml, p=NS).

Conclusion: Although multiple metabolites are concentrated in exercising muscle in CHF, only prostaglandin correlated with ergoreflex activity suggesting these factors as potential triggers to the exaggerated ergoreflex which is characteristic of CHF. This may have important implications for novel therapies to improve exercise tolerance.

P535 Desmin-free cardyomyocytes and myocardial dysfunction in end-stage heart failure

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In previous paper we demonstrated that in mild dilatative cardiomyopathy in humans, cardiomyocyte desmin disarray was associated "in vivo" with reduced actin-myosin contractile function.
The objective of this study has been to evaluate the role of desmin on myocyte contractility in end-stage heart failure.We studied 18 hearts explanted from patients undergoing heart trasplantation (10 for coronary artery disease and 8 for dilatative cardiomyopaty).Cardiac biopsies from donor's heart rapresented the control myocardium.
Immunoflorescence with desmin antibody was performed on paraffin-embebbed sections of cardiac specimens and evaluated by confocal mycroscopy.On the same samples Actin-myosin in vitro motility assay was performed in order to obtain cellular contractile function.Moreover PCR analysis of desmin in normal and pathological heart was obtained on frozen myocardial tissue.
Results: Compared to healthy cardiac tissue, in end-stage heart failure myocardium there was a significant($p<0.01$)presence of desmin -free myocytes at immunostaining with non difference between dilatative and ischemic cardiomyopathy.At PCR analysis there was a significant($p<0.03$)reduction of desmin content in disesed hearts compared to controls.Moreover there was a significant reduction of in vitro actin-myosin coupling rate in heart failure myocardium conpared to normal heart.A significant negative ($r=-0.65$; $p<0.05$) relation-ship between number of desmin-free myocytes and actin-myosyn contractile rate was found.
Conclusion: In end-stage heart failure, both fron ischemic or idiophatic origin ,compared to normal hearts,there is the presence of desmin -free myocytes. This finding is related to myocardial cellular dysfunction and could rapresent a marker of prognosis in the decision making for patients in waiting list for heart trasplantation.

P536 Left ventricular hypertrabeculation/noncompaction in 62 patients: prevalence and association with other cardiac and neuromuscular disorders

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Background and objectives: Few data are available about the prevalence of left ventricular hypertrabeculation/noncompaction (LVHT), the number of investigations necessary to diagnose LVHT and the rate of associated cardiac and neuromuscular disorders (NMD). Aim of the study was thus to assess 1. the prevalence of LVHT, 2. the number of echocardiographic examinations necessary to diagnose LVHT, 3. cardiac abnormalities are associated with LVHT and 4. the rate of NMD in patients with LVHT.
Methods: LVHT was diagnosed if in one plane >3 trabeculations apically to the papillary muscles were seen and Doppler imaging visualized intertrabecular spaces perfused from the ventricular cavity. All patients in whom LVHT was diagnosed between June 1995 to December 2001 underwent a clinical cardiological examination. It was noted, after how many examinations LVHT was diagnosed. All LVHT-patients were invited for a neurological examination.
Results: LVHT was diagnosed in 62 (12 female) patients with a mean age of 50 (18-75) years. The prevalence of LVHT was 0.24%/year. In 47% of the patients LVHT was diagnosed at the first echocardiographic examination, in 25% >3 examinations were necessary. In 97% of the patients LVHT was associated with echocardiographic abnormalities, ECG abnormalities in 92%, cardiac symptoms in 89%, heart failure in 73% and arrhythmias in 65%. Among the 49 LVHT-patients who underwent a neurologic examination, 82% had a NMD and 18% were neurologically normal.
Conclusions: LVHT is a heterogeneous echocardiographic finding which is often overlooked, more prevalent than previously believed and associated with NMD in the majority of patients.

P537 Assessment of viable tissue in Q-wave regions by metabolic imaging using single-photon emission computed tomography in ischaemic cardiomyopathy

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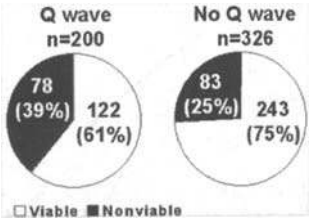
Aim: Chronic electrocardiographic Q waves are often believed to reflect irreversibly scarred, transmurally infarcted myocardium. The aim of this study was to evaluate whether residual viable tissue persists in dysfunctional myocardial regions related to chronic Q waves on the surface electrocardiogram in patients with heart failure.
Methods: A total of 148 patients with healed myocardial infarction and impaired left ventricular (LV) function presenting with heart failure symptoms underwent electrocardiography and metabolic imaging using Tc-99m-tetrofosmin/F18-fluorodeoxyglucose (FDG) single-photon emission computed tomography (SPECT). Patients with primary cardiomyopathy, significant valvular disease or left bundle branch block were excluded. The LV was divided into 4 major regions to compare myocardial viability in regions with and without chronic Q waves on surface electrocardiography.
Results: According to FDG SPECT metabolic imaging, residual viable tissue persisted in a high proportion (61%) of dysfunctional myocardial regions with chronic Q waves. Regions with chronic Q waves were more often dysfunctional than regions without Q waves. Moreover, dysfunctional regions with chronic Q waves were less frequently viable compared to dysfunctional regions without Q waves on the electrocardiogram.



Viability in infarcted regions.

Conclusion: This study demonstrates that chronic Q waves on electrocardiography in patients with heart failure do not necessarily imply irreversibly scarred myocardium. Residual viable tissue persists in a high proportion of dysfunctional ventricular regions according to FDG SPECT metabolic imaging.

P538 Human urotensin II and big endothelin in patients with chronic heart failure

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Background: Human urotensin II (hU-II) is the most potent mammalian arterial vasoconstrictor identified so far, but it has also vasodilating properties. HU-II receptors are predominant in the human heart and arterial vessels, suggesting to be of importance as a cardiovascular mediator. Aim of this study was to measure hU-II plasma concentrations in patients with and without chronic heart failure (CHF) at rest and exercise, to examine its correlation with exercise capacity and to compare it with the vasoconstrictor big endothelin.
Methods: We prospectively studied 32 patients (pts) with CHF (60 ± 12 years, 7 women, LVEF 26 ± 6%) and 10 healthy controls (54 ± 12 years, 5 women, LVEF 60 ± 4%). All CHF pts had a LVEF < 35%. Cardiopulmonary exercise testing was performed in all CHF pts and controls. Serum levels of hU-II (enzyme immunoassay, Immundiagnostik, Bensheim, Germany) and big endothelin (ELISA, Immundiagnostik, Bensheim, Germany) were measured prior to symptom-limited bicycle exercise and at peak exercise.
Results: Peak VO2 was significantly lower in CHF pts than in controls (14.7 ± 3.6 vs. 19.8 ± 3.8 ml/min/kg, $p < 0.01$). HU-II concentrations at rest were comparable in CHF pts (2990 ± 1104 pg/ml, range 1730 - 7010 pg/ml) and controls (3290 ± 508 pg/ml, range 2710 - 3750 pg/ml, n.s.). At peak exercise hU-II plasma levels were still not significantly different in CHF pts and controls (3063 ± 1185 vs. 3213 ± 1188 pg/ml, n.s.). HU-II concentrations at rest and at peak exercise showed no significant alterations in pts with CHF and controls. HU-II concentrations at peak exercise correlated better with peak VO2 in controls ($r = -0.61$, $p <0.01$) than in CHF patients ($r = 0.25$, $p <0.01$). Resting hU-II levels demonstrated no correlation with peak VO2 in controls or CHF patients. Big endothelin levels were significantly higher in CHF pts compared to controls at rest (2.8 ± 1.8 vs. 1.7 ± 0.1 fmol/ml, $p < 0.01$) and after exercise (2.7 ± 1.7 vs. 1.6 ± 0.2 fmol/ml, $p <0.005$).
Conclusions: This is the first report about in vivo studies of hU-II plasma concentrations in CHF. HU-II levels allowed no discrimination between patients with and without CHF. Physical exercise did not lead to significant changes in circulating hU-II neither in CHF patients nor in controls. In contrast, big-endothelin, an established vasoconstrictor, demonstrated significant elevation in CHF patients compared to controls at rest as well as after exercise.

P539 Why are patients with congestive heart failure due to systolic dysfunction discharged without angiotensin-converting enzyme inhibitors?

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Introduction: Although a number of well-designed prospective trials have demonstrated that ACE inhibitors improve survival in pts with heart failure (HF) due to systolic ventricular dysfunction, information exists about the under prescription of ACE inhibitors to these pts.
Purpose: To study the factors that determine prescription of ACE inhibitors in pts with HF and ventricular dysfunction discharged from our hospital
Methods: A total of 1,953 HF or related diagnosis were done among patients older than 15 years consecutively admitted to our institution during 1 year period. Their hospital records were collected and retrospectively checked. We excluded pts: a) in whom the presence of HF could not be objectively determined, b) with acute MI, c) in whom some data were not available. Echocardiography was performed in 706 pts and 381 had LVEF $\leq$0.5 (54%), 355 (93%) were discharged alive. To identify factors that prevented ACE inhibitors prescription a multivariate analysis was done.
Results The number of pts discharged on ACE inhibitors was 244 out of 355 (69%). Pts with ejection fraction < 0.30 received more ACE inhibitors than pts with ejection fraction between 0.3 - 0.4 or 0.4 - 0.5 (77, 66 and 51%, respectively, p < 0.001). Factors that prevented ACE inhibitors prescription are depicted in the table (multivariate analysis).

Variables related with no ACEi treatment

	OR (CI 95%)	p
Renal insufficiency	4.1 (2.3 -7.5)	<0.00001
Aortic stenosis *	1.8 (1.2 - 2.5)	0.002
Ventricular dysfunction**	0.55 (0.41- 0.73)	0.0001

* Codified from no=0 to severe=3.** Codified from ejection fraction 0.4-0.5=1 to ejection fraction <0.30=3Area under ROC curve: 0.77 (0.72 – 0.82)

Conclusions: Hospitalized pts with HF due to systolic dysfunction are more frequently discharged without ACE inhibitors if they have renal insufficiency, aortic stenosis or less severe systolic dysfunction.

P540 Incidence and progression of cardiac lesions in systemic sclerosis

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Background: Systenic sclerosis is characterized by fibrous thickening of the skin and associated degenerative disease of the fingers, oesophagus, bowel, kidneys, lungs and heart. This study aimed to echocardiographically investigate the frequency, severity and evolution of cardiac lesions in patients (pts) with diffuse Systemic Sclerosis (SSc).
Material and Methods: Sixty-four (60 females – 4 males, aged 59 ± 11 years) pts with SSc were evaluated with M-mode, 2D and Doppler echocardiography after a follow-up period of 42 ± 12 months. The left ventricular fractional shortening (FS) and the velocity of tricuspid regurgitant jet pius the right atrial pressure served as indices of LV systolic function and pulmonary systolic pressure. Organic valvular involvement was defined as valve thickening and/or regurgitation. Left ventricular mass index was calculated by the Penn convention formula.
Results: Left ventricular systolic dysfunction (FS<29%) was present in 8 pts (12.5%) in the first study and in 11 (17%) in the last. Valvular involvement occurred in 12 pts (18.7%) in the beginning and 17 (26.5%) in the end. Pulmonary hypertension was detected in 13 patients (20.3%) in the first and in 28 (43.7%) in the last study (p<0.05). Left ventricular mass index appeared significantly different between the two measurements (102.5 ± 22 vs 114 ± 26 g/m^2, p<0.01).
Conclusion: Our results show that the evolution of cardiac lesions in SSc is rapid, with most significant changes being pulmonary hypertension and left ventricular mass index.

P541 Haemodynamic response to dialysis in patients with chronic renal failure and impaired ventricular function

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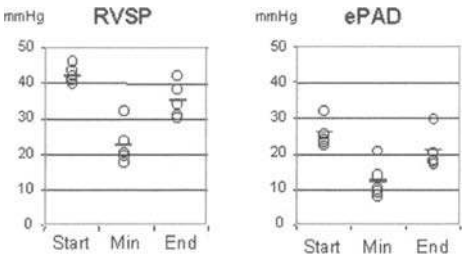
Background: Cardiovascular complications are the major cause of morbidity and mortality in patients with chronic renal failure and seem to become exacerbated after the start of maintenance dialysis. Repeated volume overload between dialysis sessions and pressure drops during hemodialysis may contribute to this.
Methods: Five patients on maintenance hemodialysis, age 53-76, with systolic and/or diastolic heart failure (EF 20-50%) received an implantable hemodynamic monitor (IHM, Chronicle® model 9520, Medtronic). The IHM consists of a memory device implanted subcutaneously and a transveneous right ventricular (RV) lead carrying a pressure sensor placed in the RV outflow tract. It continuously records heart rate, RV systolic (RVSP) and diastolic pressures (RVDP), pulse pressure, dP/dt and an estimate of pulmonary artery diastolic pressure (ePAD).
Results: RVSP and ePAD dropped by 35-45% during all dialysis sessions in each patient, irrespective of systolic and diastolic LV dysfunction. This drop occurred immediately after start of dialysis and was partly restored at termination. Between dialysis sessions, cardiac filling pressures reached levels typically seen in heart failure (RVSP at start of dialysis 42 ± 3 mmHg). The figure shows mean RVSP and ePAD values during dialysis (min = minimum pressure).



Pressure changes during dialysis.

Conclusion: The observed cyclic changes in right ventricular pressures during dialysis could have a detrimental effect on ventricular performance. Whether the pressure recordings from the monitor may help in optimising the dialysis protocol to avoid these pressure changes remains to be determined.

P542 Fail of non-invasive evaluation of flow-mediated vasodilation in the differentiation between ischaemic and non-ischaemic dilated cardiomyopathy

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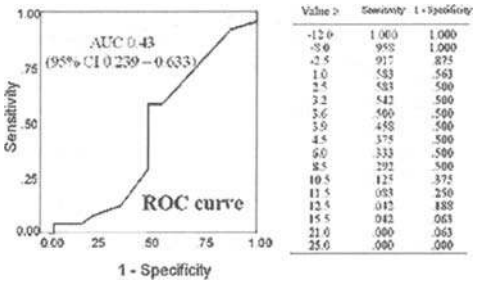
Recently, high frequency transducers have been introduced in the Echo Labs to non-invasively measure flow-mediated endothelial function. Aim of the study was to evaluate whether endothelial dysfunction assessed by this method could differentiate ischemic from non-ischemic dilated cardiomyopathy (DC).
Methods: 40 patients with DC undergoing cardiac cath were studied. Flow-mediated brachial artery vasodilation was measured using high-frequency transducers (Agilent 5500 or Aloka SSD 870 equipments). ROC curves were constructed in order to identify whether any cut-off could differentiate between ischemic and non-ischemic DC.
Results: Out of the 40 patients, 24 (60%) had ischemic, and the remaining 16 (40%) non-ischemic DC. Patients with ischemic DC had a significantly higher basal brachial artery diameter, but there were not significant differences between endothelial function between both groups. Moreover, ROC curve did not provide any cut-off that could be of help in differentiating between both groups (see table and figure).

Ischemic vs non-ischemic DC

	Non-ischemic DC	Ischemic DC	p
Basal brachial artery diameter (mm)	3.97±0.56	4.37±0.60	0.04
Hyperemia diameter (mm)	4.18±0.47	4.54±0.72	NS
% brachial vasodilation	6.00±8.07	3.97±6.25	NS
Endothelial dysfunction	8 (50.0%)	15 (62.5%)	NS



ROC curve.

Thus, the non-invasive evaluation of flow-mediated endothelial function is not useful in the differentiation between ischemic and non-ischemic DC.

P543 Spectrum of risk factors and comorbidity in a hospitalized population with congestive heart failure

M. Martínez-Sellés[1], J.A. Garcia Robles[1], L. Prieto[2], J.A. Serrano[1], R. Muñoz[1], E. Frades[1], J. Almendral[1]. [1]*Madrid, Spain;* [2]*Universidad Complutense, Biostatistics Dept., Madrid, Spain*

Introduction: The progressive aging of population along with increased survival of patients with ischaemic heart disease and high blood pressure, as a result of improvements in treatment, are leading to increasing prevalence of congestive heart failure (CHF) mainly in the elderly. The aim of this study was to investigate the frequency of comorbid diseases in hospitalized CHF patients.
Methods: A total of 1953 CHF or related diagnosis were done among patients older than 15 years consecutively admitted to our institution during 1 year period. Their hospital records were collected and retrospectively checked. We excluded 454 patients that did not fulfill the established criteria of CHF, 69 patients with acute myocardial infarction and 72 patients in whom some data were not available. Therefore we studied 1358 admissions in 1075 patients (1.27 admission per patient).
Results: Mean hospitalization time was 16 ± 15.5 days (median 12 days). Mean age was 74.7 ± 11.6 years and 42% were men.
Risk Factors: Hypertension (43%), diabetes (30%), smoking (16%) and hyperlipidemia (11%).
Comorbidity: A. Cardiovascular diseases: atrial fibrillation (AF)(49%), previous myocardial infarction (15%), previous stroke (12%), left bundle branch block (11%), severe coronary stenosis (9%), right bundle branch block (8%), valvular surgery (7%), pacemaker (7%), peripheral vascular disease (6%) and CABG (4%). B. Systemic diseases: chronic pulmonary disease (CPD)(30%), renal disease (14%), alcoholism (8%), ulcer disease (6%), severe obesity (6%), dementia (6%), liver disease (5%) and cancer (4%).
Conclusions: The majority of our hospitalized patients with CHF are women, and have an advanced age, and long admissions. We found frequent multiple comorbidity, prevalence of AF, CPD, diabetes and renal disease among patients admitted with CHF was particularly high.

P544 Neurohumoral effects of weight loss in surgically treated obese patients

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Obesity may cause major changes of the neurovegetative balance with an increase in the sympathetic drive which may have an important role, not only in the pathogenesis of obesity, but also in the development of cardiovascular diseases and cardiac death. In this study we used power spectral analysis (PSA) of heart rate variability (HRV) and plasma levels of catecholamines to test the hypothesis that weight loss may reverse obesity related disturbances in cardiovascular autonomic function.
Thirty-three obese patients (mean body mass index, 47.8; mean age, 38±10 years) were studied by PSA of HRV at baseline and after a 50% loss of the excessive body weight (BW), compared to the ideal one, obtained by surgical therapy. The total power (TP) of HRV, its low frequency (LF) and high frequency (HF) components and the LF/HF ratio were measured in basal conditions, during spontaneous breathing, during vagal stimulation by controlled breathing and during sympathetic stimulation by mental stress test. Plasma levels of norepinephrine and epinephrine were assessed with the patient in the resting condition. During spontaneous breathing, weight loss caused a significant reduction in the LF ($P < 0.001$) with a concomitant increase in the HF ($P < 0.0001$) component and a reduction in the LF/HF ratio ($P<0.001$). Vagal stimulation by controlled breathing caused a significant reduction in the LF ($P<0.005$) and an increase in the HF ($P<0.05$) component of HRV, at baseline, before weight reduction, with a further, highly significant, increase in vagal drive shown by the further reduction in the LF/HF ratio ($P<0.00001$), after weight loss. Sympathetic stimulation by mental stress did not cause any significant change of the LF component, at baseline. In contrast, weight loss was associated with a significant increase in the LF/HF ratio during mental stress ($P<0.0001$). Thus, weight loss was associated with an increase of both the vagal and the sympathetic responses. Assessment of plasma catecholamines showed a significant decrease in both plasma norepinephrine and epinephrine levels after weight loss (from 538±131 to 253±42 pg/ml and from 228±113 to 55±6 pg/ml, respectively, $p<0001$ in both cases).
In conclusion, we have shown that obese patients have an increase in the sympathetic drive at baseline, with a very low response to sympathetic stimulation. Weight loss reduces the LF/HF ratio, with a concomitant increase in the response to both sympathetic and vagal stimulation. These favorable hemodynamic and functional changes are attended by a significant reduction in cathecolamine plasma levels.

P545 Elevated left ventricular filling pressures and impaired alveolar-capillary diffusion capacity in chronic heart failure: any link?

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Background: In chronic heart failure (CHF) the occurrence of an impaired alveolar-capillary diffusing capacity, as assessed by carbon monoxide technique (DLco), is well established. Specifically, an increased resistance to gas exchange negatively affects the clinical status and exercise performance of these patients. The relationship between the increased left ventricular filling pressures (FPs) and a reduced DLco has not been characterised before. We aimed at evaluating whether, in CHF, higher FPs are associated with an abnormal DLco.
Materials and Methods: 21 CHF patients (male/female: 19/2; mean age 63±9 years) with an average EF of 36%±11% underwent clinical, echocardiographic and metabolic stress testing evaluation. Alveolar gas exchange was also investigated by measuring DLco, analysing its membrane (DM) and capillary volume (Vc) components. FPs were measured by combining transmitral [(early diastolic flow (E) and late diastolic flow (A)] and pulmonary venous flows and peak velocity of mitral anulus pulsed tissue Doppler velocity-time (TDI) waves (means of septal and lateral velocities) in systolic phase (TDIs), and early (TDIpd) and late diastolic phase (TDItd). Accordingly, patients were divided in 2 groups: group 1, with normal FPs (transmitral peak E/A velocities <1.2 and E deceleration time >150 msec; pulmonary venous systolic/diastolic integrals >1; E/TDIpd ratio <10) and group 2 with high FPs (transmitral peak E/A velocities>1.2 and E deceleration time <150 msec; pulmonary venous systolic/diastolic integrals<1; E/TDIpd ratio >10).
Results: Group 1 compared to Group 2 presented with an higher DLco (25.5±7.0 vs 16.7±6.0 ml/min/mmHg; $p<0.01$), DM (32.7±6 vs 24.5±9 ml/min/mmHg; $p<0.05$), TDIs (12.8±3.3 vs 8.8±1.0 cm/sec; $p<0.05$), TDItd (13.2±5.5 vs 9.3±3.3 cm/sec; $p<0.05$) and a reduced E/TDItd (4.4±2.1 vs 7.6±3.5; $p<0.05$). By using the Receiving Operating Characteristic (ROC) methodology a DLco cut-off of 21 ml/min/mmHg was identified. This cut-off separated group 1 from group 2 with a high specificity (73%) and sensitivity (87%).
Conclusions: CHF patients with higher FPs present with an increased resistance to gas exchange. Putative diastolic mechanisms sustaining an increase in FPs seem to be the same background for the development of gas exchange abnormalities and DLco impairment.

P546 Cardiac calcification is highly predictive for increased mortality in younger patients with congestive heart failure: prospective follow-up study

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Objectives: Multiple cardiac calcifications are much less frequently observed in younger pts and although their presence is generally associated with adverse cardiovascular outcomes, it is unclear whether they increase mortality in younger pts with CHF.
Methods: We prospectively studied 469 consecutive pts (199 males, 270 females, mean age 72±9y) admitted to hospital due to congestive heart failure (NYHA II-IV). Univariate and multivariate analyses were performed to test the association between the presence of aortic valve sclerosis (AVS), aortic root calcification (ARC) and mitral annular calcification (MAC) detected by 2D echocardiography, and total mortality during a follow-up in pts with CHF younger and older than 65y. The mean follow-up was 28±7 months.
Results: 110 pts (23%, mean age 56±6y) were younger than 65y and 359 pts (77%, mean age 76±6y) were older. The younger pts, compared to the older, had significantly higher BMI (30.3 and 27.9, resp., p=0.001), a larger left atrium (4.8 cm and 4.5 cm, resp., p=0.001), a higher uric acid (485.5 and 451.9, resp., p=0.05) and triglycerides (1.67 and 1.44, resp., p=0.05). Older pts had significantly more frequently MAC (p=0.05), AVS (p=0.0001), ARC (p=0.0001), as well as the combination of MAC+AVS+ARC together (0.0001). No diferences were observed in other risk factors including LVEF. In therapy, younger pts had more statins and calcium channel blockers (p=0.005 and 0.05) compared to older pts. During the follow-up 24 (22%) pts died in the younger group compared to 175 (49%) in older group (p=NS). Using the Kaplan-Meier survival curve model there was a 19% increase of total mortality (log rank = 47.3, p=0.0001) in pts with the presence of MAC+AVS+ARC compared to those without this finding. In the younger group, there was an even higher increase of mortality (24%, log rank = 27.6, p=0.0001). After adjusted multivariate Cox proportional-hazard analysis, age (OR 1.06, p=0.0001, 95% CI 1.03-1.08), MAC+AVS+ARC (OR 2.64, p=0.005, 95% CI 1.40-3.47) and uric acid (OR 1.14, p=0.05, 95% CI 1.05-1.23) were the only independent predictors of increased mortality in the whole group of pts. In younger pts OR of MAC+AVS+ARC was much higher (OR 16.0, p=0.0001, 95% CI 5.03-51.17).
Conclusion: Younger pts with CHF and multiple cardiac calcifications have a 16-times higher risk of death compared to those without calcifications. Therefore, multiple cardiac calcifications should be considered as a powerful independent predictor of increased mortality particularly in younger pts with CHF.

P547 Does the degree of hyperglycemia influence diastolic myocardial function in patients with type 2 diabetes?

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Diastolic left ventricular function is impaired in patients with diabetes mellitus. The relationship of glucose control to diastolic function has not been well defined in D patients. We tested the hypothesis, that the degree of hyperglycaemia influences diastolic myocardial function in patients with type 2 diabetes (D).
Methods: 33 D (mean age 59±8 years) had systolic (Vs) and diastolic (Vd) regional myocardial velocities assessed with pulsed Doppler tissue imaging in 12 left ventricular segments. Subgroups were defined according to the diagnosis or exclusion of ischemic heart disease by dobutamine stress echocardiography (SE). 25 D were studied before and after 3 weeks of improved metabolic control and 7 D with unchanged treatment and unchanged metabolic control (C).
Results: In the 9 patients with normal SE, there was a significant negative correlation between Vd and age (r=0.85, p<0.003) and Vd and fasting blood glucose (r=0.76, p<0.02) before and after improved metabolic control (r=0.83, p<0.006 and r=0.87, p<0.002) respectively. The remainders did not demonstrate such correlation as ischemic heart disease impairs Vd independently. In C, fasting blood glucose, Vd and Vs remained unchanged. After improved metabolic control, fasting blood glucose decreased by 3.7±2.7 mmol/L, Vd increased from 7.9±1.6 cm/s to 8.8±1.7 cm/s (p<0.01) and Vs remained unchanged (6.2±1.0 and 6,6±0.9 cm/s). The changes in Vd were significantly correlated to the change in fasting blood glucose after improved metabolic control in all patients: r=0.53, p<0.002.
Conclusion: Diastolic dysfunction in diabetic patients is influenced by the degree of hyperglycaemia and, additionally, ischemic heart disease and by increasing age. Strict glycemic control, however, may augment Vd in all these states.

P548 Effect of folate supplementation on allograft vascular disease after one year from heart transplant: a prospective randomized trial

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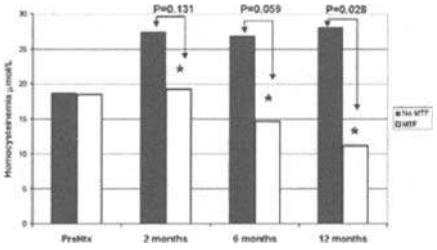
Introduction: Graft vascular disease (GVD) is a major determinant of mortality in heart transplant (HT) recipients. High serum homocysteine (tHcy) levels may enhance GVD progression. Although folate supplementation decreases tHcy, it is unknown whether folate may directly influence GVD progression. This prospective randomized study aimed to examine the effect of calcium 5-n-methil-tetrahydrofolate (MTF) administration on GVD detected by intravascular ultrasound (IVUS).
Methods: 29 consecutive HT recipients (79% males, aged 53±12, 37% with ischemic cardiomyopathy) randomly assigned to receive MTF 15mg. Serum levels of tHcy were determined before HT and 2, 6 and 12 months after HT. Complete lipid panel was also determined. IVUS of left anterior descending (LAD) was performed after 1 and 12 months from HT. Planimetry of intimal area (IA) was performed in serial cross sectional images chosen every 2 mm in proximal 30mm of LAD.
Results: 14 patients received MTF and 15 did not (P>0.1 for all baseline characteristics). Mean tHcy increased after HT only in non-MTF patients, while it decreased significantly in those assuming MTF (Figure; *P<0.05). Average IA increased in patients assuming MTF (1.87±3.26 vs. 3.41±3.31 mm^2; P<0.01) as well as in those not assuming MTF (1.85±2.73 vs. 3.42±3.31 mm^2; P<0.01). LDL serum levels correlated with the increase in IA(P=0.037), while tHcy plasma levels did not (P=0.632).



Homocysteine levels and MTF assumption.

Conclusions: The preliminary results of this prospective randomized trial suggest that although MTF significantly decreased tHcy after HT, it is ineffective in preventing intimal growth in graft coronary arteries after 12 months of follow-up. LDL concentration resulted a major non-immunological determinant of GVD in HT recipients.

P549 Prognostic impact of coronary endothelial dysfunction after heart transplantation

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Cardiac allograft vasculopathy (CAV) is the most aggressive atherosclerosis in humans. Coronary endothelial dysfunction may predict future progression of coronary intimal thickening in heart transplant patients. We analyzed the prognostic impact of epicardial and microvascular endothelium-dependent and endothelium-independent vasomotor function in 188 human heart transplant recipients. Functional coronary measurements were performed 25±30 months after heart transplantation. Coronary endothelial dysfunction was defined as >10% epicarial vasoconstriction and/or <100% coronary flow increase in response to ACh. Patients were followed up for 36±20 months (1-8 years). Cardiovascular related events (CVRE) and death were analyzed. Over the course of the study, 15 patients developed CVRE (8%) and 19 patients died (10%; n=9 with cardiovascular related death). Patients with coronary endothelial dysfunction at baseline had significant more events during follow-up (CVRE p=0.023; death p=0.019) compared to patients with normal endothelial function. Endothelium-independent vasomotor response was not related to CVRE or death during follow-up.
Allograft coronary endothelial dysfunction predicts CVRE and death after human heart transplantation. Early studies of endothelial function may play an important role in predicting clinical outcomes after transplantation.

P550 Sleep-related breathing disorders in patients with stable heart failure

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Background: Sleep-related periodic breathing with recurrent episodes of apnea and hypopnea is known to occur in patients with heart failure. Recent data suggest that sleep apnea can also lead to the progression of cardiac dysfunction in patients with chronic heart failure. However, few studies of sleep apnea in heart failure have been reported and studies with historical and physical findings and laboratory examination are needed.
Aims: To analyze the impact of sleep-related breathing disorders (SRBD) in ambulatory patients with stable heart failure.
Method: We consecutively studied 54 patients with stable heart failure due to systolic dysfunction (left ventricular ejection fraction <45%) who were clinically stable (symptoms or signs of heart failure had not changed in the previous 4 weeks) and received standard therapy. Baseline assessment included: specific cardiopulmonary questionnaire, radionuclide ventriculography, shuttle walking test (SWT) and quality of life questionnaires: functional outcomes of sleep questionnaire (FOSQ) and Minnesota living with heart failure questionnaire (MLHQ). All patients underwent a full-night polysomnography. SRBD was defined with an apnea-hipopnea (AHI)>10 in three categories: central (C), obstructive(O) or mixed(M). A SBD in which greater than 50% of events were central was defined as central sleep apnea; if >50% of events were obstructive, it was defined as obstructive sleep apnea.
Results: According to the AIH threshold, 20 patients (37%) had SRBD (AHI 28.4 ± 4.4; 17 (85%) with central apneas and 3 (15%) with obstructive apnea) and 34 patients (63%) had not SRBD (AHI 3 ± 0.5).There were no significant differences between both groups in age, sex, body mass index, left and right ventricular ejection fraction. We found differences statistically significant in MLHQ (29.5 ± 3.6 vs 15.4 ± 5.5. p<0.001), FOSQ (71.6 ± 5.5 vs 84.4 ± 3, p<0.001), SWT (229.4 ± 54.2 vs 445.1 ± 45.4, p<0.05) and hospital admissions due to heart failure (90% vs 39.4%, p<0.001) between the group with SRBD and the group without SRBD.
Conclusions: The prevalence of severe occult SRBD is high in ambulatory patients with stable and optimally treated heart failure. These selected population have less exercise tolerance and worse quality of life than those patients without SRBD.

P551 Prevalence of heart failure and asymptomatic ventricular dysfunction in an urban sample of Portuguese adults – preliminary results

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Objective: To measure the prevalence of heart failure and asymptomatic ventricular dysfunction in a community sample of adults living in Porto, Portugal.
Participants and methods: A cross-sectional study is being conducted to measure the prevalence of heart failure (HF) and asymptomatic ventricular dysfunction in a random sample of adults of both genders, aged 45 years or more and living in Porto. Participants were selected by random digit dialing and attended an interview with a physician, in which a structured questionnaire was used to assess the presence of symptoms, and physical examination, ECG and echocardiogram were performed. Heart failure was diagnosed according to the criteria of the European Society of Cardiology; cardiac dysfunction was defined as left ventricular ejection fraction lower than 45% and/or valvular disease of at least moderate severity.
Results: We have evaluated 354 individuals. In 30 (8.5%) it was not possible to calculate the ejection fraction (EF) due to the bad quality of the acoustic window. Among the remaining 324, we identified 7 with EF<45% and 5 with valvular disease(1 patient fulfilled both criteria). Seven of these individuals were symptomatic yielding a prevalence of HF (95%CI) of 2.2% (0.9%-4.4%) in this population. Of the 7 patients with ventricular dysfunction, 4 had no symptoms (prevalence of asymptomatic ventricular dysfunction of 1.2%, 95%CI 0.3%-3.1%). In the assessed population, 17 participants had EF between 45 and 50% (minimally depressed systolic function), and among these 7 had symptoms (1 had chronic respiratory disease, 1 was obese and 5 had no other cause for symptoms). Thus, the prevalence of HF with minimally depressed systolic function was 1.5% (0.5%-3.6%).
Conclusion: These preliminary results show that in our community the prevalence of HF is similar to that reported in studies conducted in other European populations with similar characteristics. We found a prevalence of HF with minimally depressed systolic function very close to that of HF.

P552 Process-of-care measures and quality-of-care assessment in an heart failure outpatient setting

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The achievement of measurable, rapid and sustainable improvement in quality-of-care (QoC) of patients with heart failure (HF) is a challenge for stake-holders and individual health care providers.
In order to assess the QoC provided in an HF outpatient clinic, we evaluated a series of evidence based process-of-care measures in clinical practice.
Methods Medical records of 169 consecutive pts referred to our HF clinic with at least 2 visits have been reviewed. The measures considered were inspired by the Veterans Affairs proposal (CHF QUERY; Circulation 2000;101:e122): left ventricular ejection fraction (LVEF) and aetiology assessment, ACE-inhibitors and beta-blockers (BB) if LVEF <41%, spironolactone if NYHA III-IV, anticoagulants or antithrombotics if atrial fibrillation or if ischemic aetiology, statins if ischemic aetiology and LDL>100 mg/dL, blood pressure control (<140/90 mmHg), patients adherence to prescriptions (daily weight and/or blood pressure monitoring).
Results 121 pts were in NYHA class I-II (63%), 39 in III (23%) and 7 in IV. Aetiology of HF was assessed in 93% pts (56% ischemic, 9% valvular, 12% idiopathic, 15% other). LVEF was measured in all pts (LVEF 33±11%; <41% in 135 pts). Among pts with LVEF <41%, 121 (90%) received ACE-inhibitors; 13 did not for contraindication (creatinine >3.0 mg/dL in 10, hypotension in 3) and 1 for neutropenia onset. In the same group BB were prescribed in 49 pts (64%), but the treatment was withdrawn in 4 pts and was contraindicated in 37 (COPD in 8, severe peripheral vascular disease in 10, hypotension in 12, bradycardia or A-V block in 7). Spironolactone was prescribed in 26 (45%) of the 47 pts in NYHA III-IV; it was contraindicated in 16 pts (hyperkaliemia in 14 and gynecomastia in 2). In 3 out of 95 pts with ischemic aetiology antithrombotics or anticoagulants were not prescribed (contraindicated in 1). Among pts with ischemic aetiology and cholesterol LDL >100 mg/dL, 10 (10%) were not receiving statins; the treatment was withdrawn in 1 for CK, GOT, GPT increase. Atrial fibrillation was present in 29 pts: all were receiving anticoagulants (70%) or antithrombotics (30%). An adequate blood pressure control was achieved in 133 pts (79%). Patients adherence was evaluated in 126 pts (75%) and was considered poor in 42 (33%).
Conclusion Periodic process-of-care assessment is useful in evaluating quality of care and represents a stimulus for continuous quality improvement. Among process-of-care measurements considered, the rate of BB prescription and the degree of patient adherence remain the most defective in clinical practice.

P553 Correlation of morphological and functional parameters of the skeletal muscle with a reduced electromyographic activity in chronic heart failure

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Exercise intolerance and early muscle fatigue are key symptoms in patients (pts) with chronic heart failure (CHF). In advanced stages of the disease, profound metabolic abnormalities have been described finally leading to a catabolic state with a progressive loss of muscle bulk. Aim of this study was to investigate morphological, functional and electromyographical parameters of the skeletal muscle in pts with CHF.
17 patients with CHF and 12 age-matched controls (LVEF 25±2 vs. 68±1%, BMI 26.6±0.8 vs. 28.0±1.0 kg/m^2; p=NS) were included in this study. Cross-sectional area (CSA) of the thigh was assessed by computed tomography. Under electromyographical control, maximal and 30% submaximal isometric strength as well as the relative decrease of muscle strength of the quadriceps muscle over a period of 20 s were determined. Serum levels of TNFalpha were measured by immunoassay.
Pts with CHF showed a significant reduction of muscle CSA (134.8±5.3 cm^2 vs. 165.2±7.4 cm^2, p=0.002) as compared to controls. The maximal quadriceps muscle strength was found to be significantly reduced in patients with CHF (226.7±22.3 N vs. 286.9±17.1 N, p<0.05) who also exhibited a higher extend of muscular fatigability (-2.18±0.33 N/s vs. -0.54±0.20 N/s, p<0.01). Electromyographic activity at 30% submaximal contraction showed a reduced increase in pts with CHF (66±22% vs. 114±36%; p<0.05) indicating an impaired muscle fiber recruitment. Furthermore, a significant correlation between muscular fatigability and reduced electromyographic activity was found in CHF (r=0.84; p<0.001).
Our findings demonstrate an impaired electromyographic activity and muscular function in patients with CHF suggesting a new pathomechanism contributing to functional abnormalities of the skeletal muscle in advanced stages of this disease.

P554 Airways resistance in chronic heart failure measured by impulse oscillometry

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Background-Patients with chronic heart failure (CHF) complain of breathlessness and fatigue on exertion and have reduced peak oxygen consumption (pVO2) and an increased ventilatory response (VE/VCO2 slope) when subjected to exercise testing with metabolic gas exchange. These abnormalities correlate with abnormalities of basic spirometry (FEV1 and FVC).
Methods-Impulse oscillometry (IOS) measures airways resistance and lung compliance during normal breathing and is therefore independent of respiratory muscle strength and patient compliance. Sound waves of varying frequencies produced by a loud speaker are sent into the lungs and the amplitude and phase shift of the reflected waves can be measured to give an assessment of airway resistance (R) and reactance (X).
Objective-The aim of this study was to establish whether there is increased airways resistance in patients with CHF using IOS.
Methods-23 patients with CHF and 18 controls underwent peak exercise testing with metabolic gas analysis (Oxycon Record, Jaeger, Germany) and, on a seperate occasion, had airways resistance assessment using the Jaeger (Germany) IOS system before and after a fixed period of exertion on a cycle at 25W.
Results-Patients had a lower pVO2 (18.7 (4.0) v 39.2 (8.3)ml/kg/min $p<0.0001$), elevated VE/VCO2 slope (41.6 (8.1) v 27.4 (2.9)), and lower FEV1 (2.4 (0.4) v 3.2 (0.7)l/min $p=0.0001$) and FVC (3.3 (0.7) v 4.1 (1.1)l $p<0.005$) when compared with controls. Measures of R and X correlated closely with spirometric abnormalities, and were significantly different between patients and controls (R at 5Hz 0.44 (0.16) v 0.30 (0.15)kPa/(l/s) $p<0.005$ and X at 5Hz -0.16 (0.08) v -0.09 (0.08)kPa(l/s) $p<0.05$). They also correlated with pVO2 (0.46 $p=0.0025$) and VE/VCO2 slope (0.43 $p<0.05$). There was no significant deterioration in airways resistance after exercise.
Conclusion Conclusion-Patients with CHF have elevated airways resistance and reduced lung reactance measured with IOS when compared with controls.

P555 Prevention of myocardial fibrosis by inhibition of the ubiquitin-proteasome system

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Background: Myocardial fibrosis is a hallmark of cardiac remodeling contributing to left ventricular dysfunction. The ubiquitin-proteasome system is the major pathway for intracellular protein degradation and plays a key role in degrading central signal mediators, which are likewise involved in the development of cardiac fibrosis. We have investigated whether inhibition of the proteasome may influence myocardial fibrosis.
Methods and Results: Effects of proteasome inhibition on myocardial fibrosis were studied in spontaneously hypertensive rats (SHRs). Long-term treatment over 12 weeks with the specific proteasome inhibitor MG132 (daily 1 mg/kg, n=10/group) was well tolerated and resulted in pronounced inhibition of cardiac fibrosis by -38% as revealed by computer-aided morphometry. Inhibition of myocardial fibrosis correlated with improved left ventricular function in the MG132-treated group, in comparison to control SHRs as analyzed by measuring left ventricular end-diastolic pressure (LVEDP), dp/dtmax, and dp/dtmin. Treatment of rat primary cardiac fibroblasts with MG132 (0.1 and 1 μM) revealed concentration-dependent inhibition of fibroblast growth, as well as specific and concentration-dependent downregulation of collagen I alpha 2 by as much as -73%, and collagen III alpha 1 by as much as -91%, as determined by real-time PCR analysis.
Conclusion: We conclude from these proof-of-principle experiments that inhibition of the proteasome system effectively prevents myocardial fibrosis in SHRs, a result which corresponds to improved cardiac function. These effects are presumably mediated by reduced growth and collagen expression of cardiac fibroblasts.

P556 Prolonged rat heart allograft survival after treatment with pentoxifylline

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Background: Data from multiple studies suggest that proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) are important modulators of allograft rejection. Increased levels of proinflammatory cytokines have been detected in rejecting allografts in both clinical studies and animal models, and inhibition of these cytokines has been associated with prolonged allograft survival. Pentoxifylline, a methylxantine phosphodiesterase inhibitor commonly used to treat peripheral vascular disease, has been shown to decrease the level of proinflammatory cytokines such as IL-12, TNF-alpha and IFN-gamma. We xamined the effect of Pentoxifylline on allograft rejection.
Methods: Heterotopic abdominal transplantation from Fisher 344 rats to Wistar Kyoto rats was used as a model of cardiac allograft rejection (n = 15). Wistar Kyoto to Wistar Kyoto served as controls (n = 15). In the experimental groups, recipients were intraperitoneally injected with Pentoxifylline (25mg/kg) just after operation, followed by daily injection of the drug. Allograft survival was determined by palpating heartbeats.
Results: In the control group, the mean graft survival was 21 $\pm$ 5 days. Pentoxifylline significantly prolonged the survival period (up to 70 $\pm$ 44 days, $p < 0.01$).
Conclusions: These results suggest that Pentoxifylline can be used as an effective agent in preventing graft rejection.

MYOCARDIAL FUNCTION IN HEART FAILURE

P557 Does preservation of radial function of the left ventricle compensate for loss of longitudinal function with age?

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Left ventricular (LV) performance is a combination of radial function due to concentric myocardial fibres, and longitudinal function due predominantly to subendocardial fibres. Global diastolic function declines with age, whereas systolic function is thought to be preserved, but the separate contributions of radial and longitudinal fibres are unclear. Tissue Doppler measurements of regional myocardial velocities during contraction and relaxation allow separate assessment of radial and longitudinal, and systolic and diastolic, function.
Aim: To investigate changes in radial and longitudinal function with age, at rest and during stress, in a large normal population.
Method: 110 normal subjects aged 21-84 years (32 normal volunteers, and 78 healthy patients referred for chest pain but with normal exercise ECG and coronary arteriography) were studied at rest and during dobutamine infusion (5-40 μg/kg/min, $\pm$ 1 mg atropine), as part of the MYDISE study. Digital image loops of colour tissue Doppler (GE Vingmed System V) were analysed off-line (Echopac TVI). Myocardial peak systolic velocity (S) and peak early (E) and late (A) diastolic velocities, were averaged from 2 beats. Radial function was assessed from the velocities of the basal posterior wall in a parasternal view, and longitudinal function from average velocities of 4 basal segments (septal, lateral, anterior, and inferior) in apical views. Systolic functional reserve (SFR) was calculated as the absolute increase in velocity from baseline.
Results: Correlation coefficients of resting velocities and SFR against age are given in the table (*$p<0.01$).

Velocities against age

	S wave	E wave	E/A ratio	SFR
Longitudinal	-0.38*	-0.69*	-0.69*	-0.42*
Radial	-0.03	-0.25*	-0.33*	-0.38*

Conclusion: There is a progressive and subclinical decline in systolic longitudinal (subendocardial) function with age. Radial function compensates at rest but not during stress. Diastolic function declines with age more steeply in subendocardial than in subepicardial fibres. These changes may contribute to the pathophysiology of LV dysfunction in the elderly and should be measured as risk factors for the development of heart failure.

P558 The within-subject variability of left ventricular dimensions in patients with left ventricular systolic dysfunction

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Background: The variability of the symptoms of heart failure is well recognized. We hypothesized that this could be due to day-to-day variation in left ventricular (LV) performance that can be measured by cardiac magnetic resonance (CMR) imaging. This would be an important consideration in the evaluation of LV measurements as well as in the design of future studies in patients with systolic dysfunction.
Methods: LV dimensions were evaluated twice, separated by at least 48 hours; by cinematographic (True-Fisp) breath-hold CMR (1.5 Tesla Siemens Sonata Magnetom) using a phased array chest coil in 14 patients with LV systolic dysfunction (heart failure (HF) group) and 20 healthy volunteers (HV). Images were evaluated by four independent and blinded observers.
Results: Mean (range) age in the HV group was 33.1 (23-51) and 69.2 (59-81) years in the HF group. Mean (SD) LV end-diastolic volume (LVEDV) in the HV and HF groups was 137 (24) and 218 (55) ml, respectively ($p<0.0001$). Mean (SD) LV end-systolic volume (LVESV) was 46.8 (12) and 131 (56) ml ($p<0.0001$), mean (SD) LV ejection fraction was 66.0 (5.2) and 38.5 (15) % ($p<0.0001$) and mean (SD) LV myocardial mass was 99.7 (25) and 178 (36) g, respectively ($p<0.0001$). Mean (SD) difference in LVEDV (delta LVEDV) between examinations was 3.08 (11.9) ml in the HV group and -3.90 (23.2) ml in the HF group ($p=0.03$). Mean (SD) delta LVESV was 0.96 (8.15) and -4.87 (15.1) in the HV and HF groups, respectively ($p=0.01$). Mean (range) Bland-Altman limits of agreement for delta LVEDV in the HV group for the 4 observers were -18.6 (-23.6 to -12.1) to 24.5 (10.1 to 38.8) ml and -49.8 (-53.8 to -47.5) to 42.9 (37.4 to 53.5) ml in the HF group. For delta LVESV, Blandt-Altman limits of agreement were -13.8 (-20.9 to -5.72) to 15.6 (5.26 to 21.7) ml in the HV group and -34.0 (-44.6 to -24.3) to 24.3 (20.9 to 29.3) ml in the HF group. Inter-observer variability for LVEDV was 8% in the HV group and 5% in the HF group. For LVESV, the values were 31% (HV) and 6% (HF), respectively. By multiple linear regression analyses, significant differences in LVEDV ($p=0.03$) and LVESV ($p=0.004$) between the two examinations were dependent on the subject type (HF) and not the observer.
Conclusion: The major determinants of LV dimensions measured by CMR in patients with LV systolic dysfunction vary significantly when compared to healthy volunteers. The effect is independent of observer variability and should be taken into account when evaluating LV dimensions in patients with LV systolic dysfunction.

P559 Ability of a novel tissue Doppler index to identify elevated left ventricular filling pressures in patients with abnormal relaxation

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Background: Patients with impaired relaxation may also have elevated filling pressures, without presenting a restrictive or pseudonormal mitral inflow pattern. No echocardiographic criteria for the detection of elevated left ventricular end-diastolic pressure (LVEDP) in the presence of abnormal relaxation are currently available.
Aim of the study was the noninvasive estimation of LVEDP in patients with evidence of delayed relaxation.
Methods: 87 consecutive patients scheduled for coronary angiography presenting with a mitral inflow pattern of impaired relaxation ($E/A < 1$) underwent left heart catheterization with invasive measurement of LVEDP and a Doppler echocardiographic examination, including Doppler myocardial imaging (DMI). Peak transmitral velocities were determined at rest and during the strain phase of a Valsalva maneuver. Peak diastolic velocities of the mitral annulus and the early diastolic myocardial velocity gradient of the posterior basal wall were obtained by DMI. We introduced a new temporal parameter: the myocardial relaxation time (MyoRT), that was calculated between aortic valve closure and the early diastolic velocity peak by DMI at the level of the lateral basal wall.
Results: Elevated filling pressures were found in 32 patients (group 1: LVEDP 20 ± 3 mm Hg, E/A 0.73 ± 0.14), while 44 patients had normal LVEDP values (group 2: LVEDP 7.5 ± 2 mm Hg, E/A 0.7 ± 0.14). A number of 11 patients with borderline LVEDP between 11-14 mm Hg were excluded. There were no differences with respect to clinical or conventional Doppler data between both patient groups. Of all DMI indices only MyoRT correlated significantly ($r = 0.38$, $p = 0.024$) with LVEDP and provided by ROC-analysis an acceptable predictive accuracy for LVEDP > 15 mm Hg (area under ROC-curve of 0.7 with a 95% CI of 0.57-0.82, $p = 0.005$). Prolonged MyoRT > 100 ms had a sensitivity of 63% and specificity of 60% for the prediction of LVEDP > 15 mm Hg.
Conclusions: Noninvasive assessment of LVEDP in patients with delayed relaxation remains a difficult clinical challenge. Only the new DMI-derived temporal index MyoRT enabled in this study a semiquantitative prediction of elevated filling pressures in patients with impaired relaxation.

P560 Contrast-enhanced Doppler echocardiography as an alternative to right-heart catheterization in patients with left ventricular dysfunction

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Noninvasive assessment of cardiac hemodynamics by Doppler echocardiography requires a reliable detection of flow velocity signals.
We sought to evaluate accuracy and reproducibility of contrast-enhanced Doppler echocardiography in the noninvasive estimation of hemodynamic variables in patients with chronic heart failure (HF) and left ventricular (LV) systolic dysfunction.
Right heart catheterization and Doppler echocardiography were simultaneously carried out in 45 consecutive patients with chronic HF and dilated cardiomyopathy (LV ejection fraction: 29±7%) in sinus rhythm. Doppler evaluation of right-sided regurgitant signals and of pulmonary venous flow (PVF) were performed both at baseline and after enhancement by intravenous injection of Levovist (2.5 grams of at 400 mg/ml). Noninvasive variables were estimated as follows: cardiac output by pulsed-Doppler of LV outflow tract, pulmonary capillary wedge pressure (PCWP) by a regression equation including mitral and PVF variables, right atrial pressure from the inspiratory collapse of inferior vena cava, systolic and diastolic pulmonary artery pressures by adding the estimated right atrial pressure to the peak and the end-diastolic pressure gradients of tricuspid and pulmonary regurgitation. Pulmonary artery mean pressure (PAMP) and pulmonary vascular resistance (PVR) were then calculated from these measurements. The interobsever variability of noninvasive measurements was assessed in 12 randomly selected patients by the physician sonographer and by an independent observer.
After contrast enhancement, optimal or near optimal PVF tracings were achieved in all patients, while measurable tricuspid and pulmonary valve regurgitation signals were obtained in 43 and 41 of 45, respectively. Strong correlations between invasive and noninvasive hemodynamic variables were found: $r=0.90$, SEE 0.45 l/min for cardiac output, $r=0.90$, SEE 3.1 mm Hg for PCWP, $r=0.93$, SEE 3.7 mm Hg for PAMP and $r=0.85$ SEE 1.0 Woods units for PVR. Interobserver measurements of PCWP, PAMP and PVR correlated closely ($r=0.99$, SEE=0.90, $r=0.97$, SEE=0.97 and $r=0.97$, SEE=0.30, respectively). By Bland-Altman analysis, the mean differences in hemodynamic measurements between the two observers were 0.8±1.1 mmHg, 1.4±1.9 mmHg and 0.2±0.3 Wood Units, respectively.
Contrast-enhanced Doppler ultrasound is accurate as well as reproducible in assessing cardiac hemodynamics in patients with chronic HF and LV systolic dysfunction and may constitute an alternative to cardiac catheterization in potential heart transplantation candidates and in critically ill patients.

P561 Atrio-left ventricular pacing for heart failure acutely improves diastolic filling by relieving diastolic ventricular interaction

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Although acute haemodynamic improvement, has been demonstrated in response to atrio-left ventricular pacing (LVP) in patients with congestive heart failure (CHF), the mechanisms underlying these benefits remain unclear. Mechanical and electrical resynchronisation are the more popular explainations. Our group has shown non-invasively that a significant proportion of patients with congestive heart failure have impaired left ventricular filling because of diastolic ventricular interaction (DVI). This physiological phenomenon wass assumed to be present when a paradoxical increase in left ventricular end diastolic volume (LVEDV) occurred in response to a reduction in right ventricular end diastolic volume (RVEDV). In health a reduction in LVEDV is seen in response to reducing RVEDV. We hypothesised that LVP would relieve diastolic ventricular interaction by inducing a phase shift allowing the left ventricle to fill prior to the right ventricle. We studied 8 male subjects with permanent LVP systems implanted for the treatment of heart failure and left bundle branch block on ECG. Using the same well-validated technique, of applying lower body negative pressure (LBNP) to reduce RVEDV, we compared the changes in ventricular volumes in response to LBNP with the pacing system turned on versus off. We measured right ventricular and left ventricular volumes simultaneously by radionuclide ventriculography. Of the group studied 4 out of 8 (50%) showed diastolic ventricular interaction as evidenced by an 18.8 ± 24.5% increase in LVEDV in response to reducing RVEDV by applying LBNP. This contrasted with a decrease of 21.9 ± 10.6% (p=0.037) seen in the 4 without DVI. In the sub-group with DVI, in the absence of LBNP, LVP increased LVEDV by 16.2 ±23.8% from baseline implying an improvement in diastolic filling. The left ventricular ejection fraction did not change (18 ± 8.4% vs., 18.3 ± 8.8%, p=0.89)indicating an increase in stroke volume. Furthermore in LVP mode the 'paradoxical' increase in LVEDV during the application of LBNP was almost abolished (0.1 ± 20.7%, p=0.038). We therefore conclude that LVP relieves diastolic ventricular interaction allowing improved diastolic filling at rest. Whether this benefit improves exercise tolerance in response to chronic LVP remains to be established.

P562 Intraventricular pressure gradients along the cardiac cycle: effects of ischaemia and modulation by afterload

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Experimental and clinical studies have shown significant diastolic intraventricular pressure gradients (IVPGs) in early as well as late diastole and their sensibility to changes in preload and ischemia. However, data about systolic IVPGs and their modulation by afterload and ischemia are lacking.

Simultaneous apical and outflow tract (OT) left ventricular pressures (LVP) were recorded in 5 anesthetized open-chest rabbits by 2 high-fidelity micromanometers. IVPGs (OT minus apical LVP) were analysed in control and progressively afterloaded heartbeats at baseline and after LAD coronary artery occlusion, along the cardiac cycle. Afterload was increased with beat-to-beat ascending aortic occlusions.

Mean IVPGs (mmHg) along the cardiac cycle in control beats, in afterloaded beats reaching 90% of peak isovolumetric LVP and during ischemia are shown in the table (IC: isovolumetric contraction; REj: rapid ejection; SEj: slow ejection; IR: isovolumetric relaxation; RFill: rapid filling; Di: diastase; AtrC: atrial contraction). During REj there was a negative IVPG in control conditions that was inverted by afterload and ischemia. IVPGs were positive during IC and SEj, absent during Di and negative during AtrC, and were not affected by afterload or ischemia. During IR the large negative IVPG was significantly blunted by afterload but not affected by ischemia. The positive gradient observed during RFill disappeared during ischemia but was not affected by afterload. DP/dtmin occurred 2.2±0.4 ms earlier and was 736±101 mmHg/s more negative in the OT in control conditions, but these differences disappeared with afterload elevation.

Mean IVPGs (mmHg)

	IC	REj	SEj	IR	RFill	Di	AtrC
Control	1.5±0.2	-0.6±0.1	0.8±0.1	-4.6±0.7	0.6±0.2	0.0±0.0	-0.5±0.1
Afterload	1.4±0.2	0.9±0.1*	0.9±0.1	-1.4±0.3*	0.6±0.2	0.0±0.0	-0.6±0.1
Ischemia	1.5±0.2	0.6±0.4*	1.0±0.3	-4.8±0.4	-0.2±0.5*	0.0±0.0	-0.5±0.2

*p<0.05 vs. control

The present study shows that IVPGs during ejection, in control conditions, parallel the aortic-ventricular pressure gradients and might favour ventricular emptying. Inversion of REj IVPGs during afterload elevations and ischemia might contribute to impaired ventricular ejection in these conditions. IVPGs during IR reflect earlier onset and faster relaxation in the OT in control conditions, which disappear with afterload elevations.

P563 Afterload-induced diastolic disfunction in the human heart and its exacerbation by systolic dysfunction and volume loading

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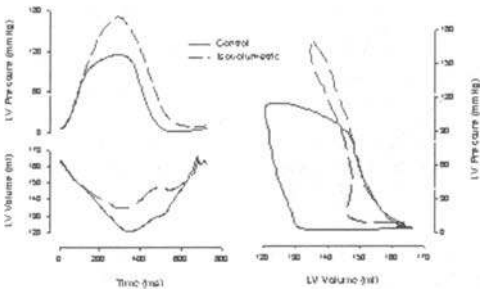
Pulmonary congestion in acute severe hypertension was recently attributed to diastolic dysfunction (NEJM, 2001). A potential mechanism underlying this phenomenon is afterload-induced diastolic dysfunction, previously described in animal models but not yet investigated in the human heart.

Twenty CABG patients (63±9 yrs) with variable degrees of systolic dysfunction (EF 25-75%) were studied prior to cardiopulmonary bypass with a pressure (n=17) or a pressure-volume (n=3) catheter. Afterload elevations were performed by clamping the ascending aorta to increase left ventricular pressure (LVP) from control up to isovolumetric. In 7 patients aortic clamping was repeated after 500cc of the priming solution.

Peak isovolumetric LVP (LVPiso) ranged from 113 to 261 (191±39)mmHg and dP/dtmax from 522 to 2399 (1208±452)mmHg/s, reflecting the variable degrees of systolic dysfunction. Afterload elevations induced diastolic dysfunction only in patients with impaired systolic function. Maximum LVP elevations (LVPiso) increased Tau 50±54% (from -37 to +160%) and EDP 3.5±2.3 (from 0 to 8) mmHg. Effects of afterload on diastolic function were inversely related with systolic function: Tau vs. LVPiso (r=-0.92, p<0.01), EDP vs. LVPiso (r=-0.96, p<0.01). Increased EDP in response to afterload elevations reflect an upward shift of the diastolic P-V relation (figure). After volume loading effects of afterload on EDP were exacerbated (7.9±3.7 vs. 3.0±1.5 mmHg) and became apparent even in patients with normal systolic function.



In conclusion, afterload-induced diastolic dysfunction is also observed in the human heart, being exacerbated by systolic dysfunction and volume loading. This mechanism might contribute to pulmonary congestion in acute afterload elevations such in severe hypertension.

P564 Analysis of dispersion of myocardial velocities by tissue Doppler echocardiography in the assessment of heart failure etiology

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Differentiating between an ischemic and nonischemic cause has important clinical implication in patients with heart failure. Several noninvasive techniques have been proposed to distinguish the two forms of cardiomyopathy, but the results are controversial and optimal strategy remains unsettled.
The aim of the study was to compare the regional heterogeneity of myocardial velocities in patients with ischemic and non-ischemic cardiomyopathy using spectral tissue Doppler echocardiography (TDE).
Study group consisted of 120 individuals- 60 patients with heart failure incl. 30 pts after myocardial infarction-MI (aged 58±10 yrs; LVEF 28±7%) and 30 pts with dilated cardiomyopathy -DCM (aged 43±12 yrs, LVEF 25±8%). Etiology was detected by coronary angiography. Control group consisted of 60 healthy volunteers (aged 43±12yrs, LVEF 65±2%). Myocardial velocities (systolic- Sm, early diastolic-Em and late diastolic-Am) were recorded with pulsed wave TDE from 3 standard apical views in the middle of 6 basal segments/pts. (lateral, anterior, posterior, inferior, anterior septum and posterior septum). To measure the regional heterogenity we calculated an index of dispersion of myocardial velocities among 6 studied walls- (V=standard deviation/mean*100%).
Results: Systolic and diastolic velocities were significantly lower in patients with heart failure than in control subjects (Sm- 4,5±1,2 vs 11,1±1,5 cm/s; Em-6,1±2,4 vs 16,6±2,2 cm/s, Am-4,6±2,0 vs 11,8±1,2 cm/s; p<0,001), but there were no significant differences in systolic and late diastolic velocities between patients with MI and DCM. The dispersion of systolic, early and late diastolic velocities was significantly higher in patients after MI than in patients with DCM (respectively; VS 32±8% vs 13±4%; VE 26±10% vs 16±5%; VA 24±11% vs 16±6%; p<0,0001). Best predictor of ischemic etiology of cardiomyopathy was dispersion of systolic velocities greater than 20% - specificity 96,8% (95%CI: 83,3%- 99,9%), sensitivity 100,0% (95%CI: 88,1%- 100,0%), PPV 100,0% (95%CI: 88,4%- 100%), NPV 96,7% (95%CI: 82,8%- 99,9%), kappa 0,97.
Conclusion: Long axis TDE velocities of the left ventricle are significantly lower in patients with heart failure. Systolic velocity dispersion index over 20% is suggestive of ischemic left ventricle dysfunction etiology.

P565 Force-frequency relationship in the echo lab: a noninvasive assessment of "Bowditch-treppe"?

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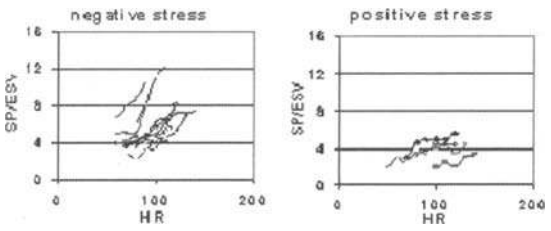
Background: Estimation of contractility of left ventricle is an important, and as yet elusive, goal with noninvasive techniques. Positive inotropic interventions are mirrored by smaller end-systolic volumes and higher end-systolic pressures. An increased heart rate progressively increases the force of ventricular contraction (Bowditch treppe or staircase phenomenon).
Aim: To assess the feasibility of a totally noninvasive estimation of force-frequency relation during stress in the echo lab.
Methods: Sixteen patients (11 males, 57±8 years) referred for exercise-echo were consecutively enrolled.Wall Motion Score Index (WMSI, 16 segment model, from 1=normal to 4=dyskinetic) was calculated. To build the force-frequency relationship, the force was determined at each step as the ratio of systolic pressure (SP, cuff sphygmomanometer)/end-systolic volume (ESV, biplane Simpson rule). The slope of the relationship was calculated with the linear best fit of the force-frequency relationship:



Results: By regional wall motion analysis, 2 groups of patients were identified: Group I (n=5) had a positive echo (WMSI baseline = 1.2 ± 0.27 vs peak stress = 1.41 ± 0.23); and group II (n = 11) had a negative echo (WMSI baseline = peak stress = 1.05 ± 0.15). The slope of the linear best fit of the force-frequency curve was lower in patients with compared to those without ischemia (Group I = 2.7 ± 1.7 x 10^{-2} vs Group II = 9.1 ± 6.3 x 10^{-2}; p=0.013): F
Conclusion: A noninvasive estimation of force-frequency relationship can be easily determined during stress echo and separates patients with and without ischemic response. This index of global contractility is theoretically appealing for identification of limited contractile reserve and latent global left ventricular dysfunction.

P566 Rate of segmental myocardial wall stress increase in dobutamine stress echocardiography – its relation with negative study and clinical symptoms

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The use of pharmacological agents such as intravenous dobutamine during stress echocardiography (DSE) changes significantly the time course of several hemodynamic and functional parameters of the left ventricular (LV) global and regional performance. Myocardial wall stress (MWS) is considered a functional quantitative parameter of regional LV function that suffers a dynamic change during DSE, and which can be evaluated using new noninvasive methods. Objective: The aim of our study was to investigate the time course changes of several segmental MWS (Kdynes/cm^2 or KPa) LV functional parameters during DSE study.
Material and Methods: MWS was calculated during both systole (S) and diastole (D) according to the general mathematical formula PA.(D+d)/4h, where PA is the S or D blood pressure, D major and d minor LV cavity diameters (mm) and h the individual segmental LV myocardial wall thickness (mm). In a group of 60 patients (pts) with a negative DSE (DSE-), mean age 57±12 yrs (43-69 yrs), 64% (35/65) males, we calculated several segmental LV functional parameters according to the ASE LV model of 16 segments. To enhance LV endocardial resolution and improve quantitation, ultrasound contrast agent Levovist® (Schering AG, Germany) was injected from baseline to peak fose, 4 gr dose, 300 mg/ml concentration. We calculated the individual value of MWS (MWSi), the mean segmental MWS (MWSm), the absolute (Var-KPa) and % (%Var-%) MWS variations, and the rate of MWSi and MWSm increases (RMWSi and RMWSm-KPa) per DSE stage (RMWS=MWSn/1-MWsn) and its mean values (RMWS/n stages), both in S and D. Data was compared among negative DSE with and without chest pain (CP-; n=35 pts vs CP+; n=25 pts).
Results: RMWS registered higher values and increase in S (1.8±0.4 KPa) compared to D (1.0±0.4 KPa; p=0.01). The basal interventricular septum (2.5±0.6 KPa p<0.01) and lateral (2.3±0.4 KPa; p<0.01) walls registered the highest RMWS values when compared to all other LV segments speciallly during the S phase. CP+ revealed higher values (S-2.2±0.4 and D-1.2±0.2KPa; p=0.01 and <0.01) when compared to CP- (S-1.4±0.3 and D-0.4±0.2 KPa) during the DSE study.
Conclusions: The LV segmental RMWS registered higher values during both the systolic and diastolic phases, increased exponentially with DSE duration and was directly related with the occurrence of chest pain during DSE, a finding that was independent of the duration of each study. Our results reflect the rate of increase of LV myocardial wall stress not compensated by the blood flow redistribution mechanisms of the subendocardial coronary microcirculation.

P567 Left ventricular geometry influences left ventricular relaxation detected by color M-mode mitral inflow propagation velocity in patients with left ventricular dysfunction

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Background: The propagation velocity (vp) of left ventricular (LV) inflow using color M-mode Doppler has been proposed as a reliable determinant of LV relaxation. The aim of this study was to assess the effect of LV geometry on vp values in patients (pts) with comparable ventricular function and different geometry.
Methods: We studied 25 pts with coronary artery disease and left ventricular aneurysm (Group 1), as well as 25 pts with dilated cardiomyopathy (Group 2). Groups 1 and 2 did not differ regarding age (mean age 64±4 vs. 60±5 yrs), LV ejection fraction (LVEF) (28±4% vs. 31±5%) and LV end-diastolic pressure (LVEDP) (16±2 vs. 17±1.5 mmHg) (all NS). Digitization of the LV endocardial borders in diastole and systole in the apical 4 and 2 chamber views was used for the study of LV geometry. As far as the segmental kinetic is concerned, the wall motion score (WMS) (the sum of segmental scores), the wall motion score index (scores sum/number of segments) and the extension of dyssynergy (percentage of dyssynergic segments) were calculated. Vp was measured as the slope of the first aliazing velocity in early diastole. All pts underwent left ventricular catheterization immediately after the echocardiographic study and the LVEDP was measured.
Results: The pts of Group 1 had lower vp than Group 2 (17±3 vs. 25±4 cm/sec). The wall motion index of Group 1 was higher than Group 2 (2.8±0.3 vs. 1.8±0.2, p<0.001). The extension of dyssynergy had negative relation to flow propagation (r=-0.63, p=0.034). Multiple regression analysis showed that the LVEDP [p=0.01, OR (CI95%): 0.97 (0.92-0.99)] and the extension of dyssynergy [p=0.04, OR (CI95%) 0.9 (0.88-0.95)] were independent factors for vp values.
Conclusions: Left ventricular geometry affects mitral inflow propagation velocity. This means that pts with left ventricular aneurysm have worse relaxation than pts with dilated cardiomyopathy. Left ventricular geometry needs to be accounted when attempting to evaluate the left ventricular diastolic function.

PERIPHERAL CIRCULATION

P568 Diagnosis of atherosclerotic carotid plaque structure and fibrous cap in vitro by IVUS, CT and MRI

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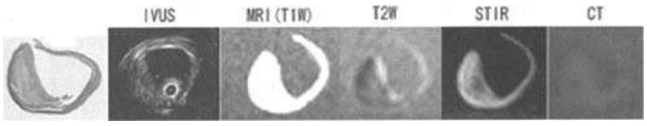
Vulnerable plaque was consisted of large lipid pool and thin fibrous cap. Using intravascular ultrasound (IVUS), we could observe plaque type and plaque distribution but lipid pool and fibrous cap could not clearly detect. The aim of this study is to investigate what is the best modality to detect atherosclerotic plaque structure and fibrous cap. We examined 4 pieces of atherosclerotic carotid arteries excised by endatherectomy. Cross sectional scanning was performed by IVUS (CVIS Insight System, Ultra Cross 20MHz; Boston Scientific Scimed, Inc) by auto-pull back method, CT (Proceed SA; GE Yokogawa Medical) by conventional method and MRI (MAGNETON (H-15) 1.5T; Siemens, Inc) by STIR imaging in addition to T1 and T2-weighted SE imaging. Each image compared with histology. Calcification of the plaque was clearly detected by IVUS but lipid pool and fibrous could not observe. MRI (T2-weighted SE imaging and STIR imaging) and conventional CT imaging could clearly detect lipid pool and fibrous cap. In terms of plaque calcification, although CT had a sensitive enough to detect plaque calcification, intraplaque structure became unclear by the effect of high CT value of the calcificaton. In comparison with these two modalities, as image quality, MRI could clearly detect intraplaque structure and thickness of fibrous cap rather than CT and as scanning time, CT was much shorter than MRI.



Atherosclerotic plaque.

In conclusion, MRI had the highest detectability of lipid pool and fibrous cap and CT was thought to have a high potential to detect plaque morphology.

P569 Impact of intravascular ultrasound, transoesophageal echocardiography and angiography guidance on aortic stent-graft placement

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Background: Endovascular stent-graft placement is a new concept of treating aortic dissection and aneurysm but there are no overall accepted recommendations for the guidance of the intervention.
Method: We directly compared angiography (ANGIO), transesophageal echocardiography (TEE) and intravascular ultrasound (IVUS) before and after implantation of 39 stent-grafts of 33 patients (9 female, 60 ± 11years) for the capability to guide the intervention in the aorta. Twenty-five patients had aortic dissection type B and 8 patient's thoracic aortic aneurysm.
Results: ANGIO, TEE and IVUS were performed without any complications in all patients. Aortic dissection: IVUS and TEE are superior to ANGIO in the identification of multiple entry (44 and 36 versus 29; $p<0.005$ each), the diagnosis of slow blood-flow in the false lumen post stent-graft implantation (26 and 25 versus 18, $p<0.005$ each) and in the detection of incomplete stentapposition (14 and 13 versus 6; $p<0.005$ each). Remaining flow in the false lumen after stent-graft implantation was detected more frequently in TEE in comparison to ANGIO (13 versus 5, $p<0.05$). In 4 patients with abdominal extension of the dissection, only IVUS was able to accurately identify the false lumen over the entire length. Thoracic aortic aneurysm: The size of the aneurysm was calculated precisely with TEE and ANGIO, not with IVUS (11 versus 4; $p<0.05$). TEE was superior to IVUS in the detection of endoleaks (4 versus 0; $p<0.05$).
Conclusion: Based on our patient data we recommend to guide stent-graft implantation in aortic dissection type B with angiography and transesophageal echocardiography and the availability of intravascular ultrasound. In complex anatomy and abdominal extension of the dissection IVUS is recommended in addition. We believe that stent-graft implantation in thoracic aortic aneurysm can be guided with angiography and transesophageal echocardiography alone, without intravascular ultrasound.

P570 Conventional vascular echography versus contrast-enhanced Doppler ultrasound of renal artery stenosis: sensibility, specificity and accuracy

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Doppler ultrasound (US) is one of many modalities that have been evaluted for the detection of renal artery stenosis. Recently the introduction of US contrast agents has substantially expanded the potential of color Doppler US. The use of echo-enhancer in combination with Doppler imaging has shown to significantly reduce the number of equivocal examinations.
The aim of the present paper has been to calculate sensibility, specificity and accuracy of conventional renal artery vascular echography (CRVE) vs renal artery contrast-enhanced Doppler Ultrasound (RCE)in blind angiographically detected arterial renal stenosis.
We have enrolled 40 pts (mean age 52 ± 8) with an angiographically detected renal artery stenosis. All the pts have been underwent in different times CRVE and RCE by using a 3,5 MHz electronic Probe (Hewlett Packard Sonos 1000). RCE have been realized giving 5-10 ml of watery suspension of Levovist as a slow bolus.
Results: see table. The valutation of renal artery stenosis has been possible in a bigger number of cases with RCE compared to CRVE (85% vs 60%). With RCE we have been obtained an increase (40% and 35% rispectivly) of Doppler signal and of color Doppler image.

n=40	feasibility	sensibility	specifisity	accuracy
RVCE	33/40	71%	78%	76%
RCE	38/40	87%	92%	89%

RVCE: conventional renal artery echography; RCE: contrast-enhanced renal artery ecography.

Conclusions: These results suggest the diagnostic effectiveness of RCE but because of major costs and prolonged duration of investigation we think that echo-enhancement is indicated when the CRVE presents a lacking quality or technical limitations

P571 The Allen and inverse Allen test, as a simple method for detecting ulnar or radial predominance. Sensitive but not specific

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Intoduction: Allen test is used broadly in order to assess ulnar artery patency during radial catheterisation procedures. The purpose of our study was to evaluate Allen and inverse Allen test sensitivity and specificity in detecting ulnar or radial upper extremity predominance, giving evidence for best and easier accessibility for cardiac interventions.
Methods: Routine coronary angiography was performed after informed consent in 49 patients, through the right femoral artery. After completion of the angiography, right brachial artery was catheterised, using the right Judkins catheter. The catheter was retrogradely inserted to the proximal end of the brachial artery, through the right subclavian artery. The right arm of the patient was in complete extension using a special supporter. Selective angiography of the upper extremity was performed, using the A-P projection. Cine films were interpreted and analyzed by two separate interventional Cardiologists and anatomic variables of both arteries were compared respectively. Radial and ulnar luminal diameter was measured at 25 mm proximal to the styloid process and pissiform bone respectively, using electronic calipers. Before catheterisation, Allen and inverse Allen test was performed in every patient and their mean time was recorded. The sensitivity, specificity, positive predictive value and negative predictive value of the Allen/Inverse Allen test for the diameter of radial artery at 25 mm compared to ulnar artery was calculated based on a 2x2 table of Allen>Inverse Allen x radial>ulnar diameter.
Results: The sensitivity of the test was estimated at the level of 90% and the specificity at the level of 50% respectively. Positive predictive value reached 73% and negative predictive value 77%.
Conclusions: Allen/inverse Allen test, an easy, cheap and no time consuming test, seem to be a quite sensitive method with a rather low specificity in detecting ulnar or radial predominance, reflecting easiest accessibility for cardiac catheterisation procedures. More elegant and costly methods are possibly needed for such decision making.

P572 Endothelial damage in atherosclerotic vascular disease by quantifying circulating endothelial cells: relationship with von Willebrand factor

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Introduction: Established atherosclerosis is associated with disturbances in endothelial function and a prothrombotic state. Furthermore severe peripheral vascular disease (PVD) manifesting as ischaemic rest pain (IRP) is related to significant morbidity and mortality. Plasma von Willebrand Factor (vWf) is an established index of endothelial damage/dysfunction. Circulating endothelial Cells (CECs) are a new index of endothelial damage, and previously been shown to be abnormal in patients with acute myocardial infarction (AMI) and unstable angina, but not in effort angina. We hypothesised that CECs would increased in patients suffering from IRP compared to healthy controls or patients with Intermittent Claudication (IC).
Methods: We studied 20 patients with IRP (15 males, age 68±10 years), 20 with IC (13 males, age 63±7 years), 20 patients within AMI <24hours (12 males, mean age 61±8 years), and 20 healthy controls (11 males, age 67±10 years). vWf was measured by ELISA. CECs were captured from EDTA/NaF whole blood using an immunomagnetic separating technique, and counted under a fluorescent microscope by an observer blinded to patient group.
Results: CECs were highest in patients with IRP and AMI, with no difference between IC and control groups (Kruskal-Wallis test, p<0.0005). The differences in vWf levels were of borderline significance between the 4 study groups (oneway ANOVA, p=0.06), with a significant difference in vWf levels between control and the IRP groups (p=0.013). There were no correlations between vWf and CECs in any of the groups.

	AMI	IC	IRP	Control	P Value
CECs (cells/ml)	4.9 (4.8-8.6)	1.1 (0.6-2.9)	3.5 (2.0-5.8)	1.0 (0.5-1.7)	<0.0005
vWf (IU/dl)	125±25	120±25	134±28	112±26	0.066

Values given as median (interquartile range) or mean ± standard deviation

Conclusion: This study demonstrates for the first time evidence of direct endothelial cell damage in severe PVD, resulting in the shedding of endothelial cells (raised CECs), perhaps indicative of tissue loss or insipient tissue loss. Such endothelial damage may contribute to the thrombotic complications of atherosclerotic vascular disease.

P573 Markers of the prothrombotic state are not increased with severity of atherosclerotic disease

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Background: Raised levels of von Willebrand Factor (vWf), a marker of endothelial dysfunction, soluble p-selectin (s-Psel), a marker of platelet activation and fibrinogen and increased plasma viscosity (PV) are known to contribute to the hypercoagulable state in atherosclerotic disease. Tissue factor (TF) is usually expressed in extravascular tissues and is part of the 'extrinsic pathway' of coagulation. Fibrinogen is also known to correlate with disease severity although vWf and s-Psel have not and little data is available on the role of plasma TF in atherosclerosis.
Methods and Results: We studied 234 patients with established atherosclerosis of the peripheral arteries defined as an ankle brachial pressure index (ABPI) of less than 0.8 (145 males, mean age 68±10 years). ABPI was taken as a marker of disease severity. Patients were split into two groups above and below the median ABPI (0.52). The vWf, TF and s-Psel were measured by ELISA, fibrinogen by CLAUSS and PV by viscometer. The table shows that other than for fibrinogen there is no difference between these markers above and below the median ABPI (unpaired t-test or Mann Whitney U test as appropriate).
Conclusion: Severity of disease does not affect the hypercoagulable state in patients with established atherosclerosis.

P574 Screening for abdominal aortic aneurysm during transthoracic echocardiography in hypertensive patients

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Aim: this study was undertaken to determine the utility of transthoracic echocardiography as a screening test for occult abdominal aortic aneurysm in hypertensive patients subjected to transthoracic echocardiography older 50 years of age.
Methods: In hypertensive patients subjected to transthoracic echocardiography, longitudinal and transverse images of the abdominal aorta were obtained during the subcostal portion of the transthoracic echocardiography. Abdominal aortic aneurysm was defined as an abdominal aortic dimension (anteroposterior or lateral) ≥ 3 cm. Exclusion criteria included prior abdominal aortic aneurysm repair, know abdominal aortic aneurysm and inadeguate images of the abdominal aorta.
Results: 180 patients met the study inclusion criteria (97 men; 83 women, mean age 73 years, range 51-90 years). An occult abdominal aortic aneurysm was identified in 14 patients (7.7%). 10 patients were men (71.4%), with a mean age of 74 years and a mean duration of hypertension of 13 years, 11 patients (78.5%) had a history of tobacco use and 3 patients (21%) had a positive family history of abdominal aortic aneurysm. All aneurysms were infrarenal in location excpet 1 (7%); the mean diameter was 3.8 cm (range 3-5.1 cm). Laminated thrombus was present in 7 patients (50%). Imaging of the abdominal aorta during transthoracic echocardiography required an average of 7.1 minutes (range 5-11 minutes).
Conclusions: Abdominal aortic aneurysm is frequently asymptomatic and often occult on physical examination. Ultrasonography is highly accurate in the diagnosis of abdominal aortic aneurysm and screening for abdominal aortic aneurysm can be readily incorporated into the transthoracic echocardiography examination. Abdominal aorta can be accurately imaged in the majority of patients (94%) undergoing transthoracic echocardiography. The present study shows that incidence of occult abdominal aortic aneurysm detected by transthoracic echocardiography in hypertensive patients older 50 years of age is significant. Screening for an occult abdominal aortic aneurysm in this patient population should be a routine extension of transthoracic echocardiography.

P575 Differentiation between ischaemic and non-ischaemic dilated cardiomyopathy by ultrasonic scanning of carotid artery with high-frequency transducers

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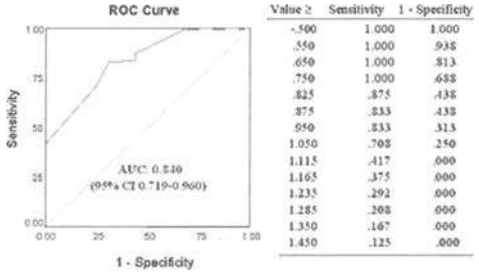
Aim of the study was to evaluate the usefulness of the non-invasive evaluation of carotid artery artery with high-frequency transducers in the differentiation between ischemic and non-ischemic dilated cardiomyopathy (DC).
Methods: 40 patients with DC undergoing cardiac cath were studied. Ultrasonic scanning of the carotid artery using high-frequency transducers (Agilent 5500 or Aloka SSD 870 machine) was performed. ROC curves were obtained in order to test the usefulness of intima-media carotid wall thickness in the differentiation between ischemic and non-ischemic DC. Also, the presence of visually detected carotid plaques was tested.
Results: Out of the 40 patients, 24 (60%) had ischemic, and 16 (40%) non-ischemic DC. Patients with ischemic DC had a significantly higher carotid artery intima thickness (1.14±0.23 vs. 0.84±0.20 mm, p<0.001). ROC curve showed a high diagnostic value of intima-media carotid artery thickness (area under the curve 0.840; see figure).



Sensitivity, specificity, and predictive values of the variables tested are shown on the table.

Diagnostic value

	Sensitivity	Specificity	Positive PV	Negative PV	Accuracy
Carotid plaques	79.2	75.0	82.6	70.6	77.5
Intima-media > 1mm	83.3	68.8	80.0	73.3	77.5
Any finding	91.7	62.5	78.6	83.3	80.0

Conclusion: Ultrasonic scanning of carotid artery with high-frequency transducers at the Echo Lab is a rapid and reliable method of differentiating ischemic and non-ischemic DC.
ROC curve

P576 Endoluminal stenting for obstructive lesions of the subclavian artery

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Background: Obstructive lesions of the subclavian artery can result in arm claudication, symptoms of subclavian steal. Surgical revascularization has been preferred method for treating these lesions. Aim: To evaluate the safety and efficacy of endovascular stenting for treating 61 obstructive lesions of subclavian artery.
Method: We performed 61 endoluminal stenting 61 patients (24males, 59±12 years). All procedures were performed with the Palmaz stents. Indications for stenting were arm claudication in 44 cases, subclavian steal syndrome in 12 cases and myocardial ischemia secondary to compromised flow through internal mammary graft in 5 cases.
Results: Procedural success (defined as abolition of pressure gradient across the aorta and subclavian artery and a residual diameter stenosis <20% without major complications (acute stent thrombosis, myocardial infarction, embolization, emergency surgery or death) was achieved in all 61 patients. All patients had symptomatic relief acutely. None of the patients had any major complications. Baseline diameter stenosis was reduced from 100% to 14.2±8.3%, mean systolic pressure difference between the upper extremities was 49.2±14.3mHg to 1.2±2.3mHg (p<0.01). In 59 of 61 patients, we performed follow-up (6 to 12 months later) angiography and these were no restenosis.
Conclusion: Endoluminal stenting of the subclavian artery is safe and effective with high technical success and excellent hemodynamic results. These were no cerebral or distal embolization.

P577 Beneficial effects of renal artery stenting on renal function in diabetic patients with chronic renal insufficiency

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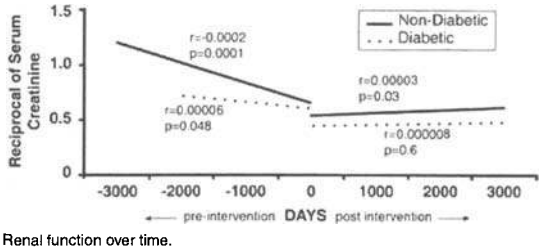
Background: Renal artery stenting has been shown to stabilize or improve renal function in a significant proportion of pts with atherosclerotic renovascular disease and impaired renal function. Whether diabetic (DM) pts obtain similar benefit as nondiabetic pts (NDM) is not known.
Methods: The renal function of 36 consecutive pts with bilateral renal artery stenoses (11 DM; 25 NDM) and renal insufficiency (serum creatinine ≥ 1.5 mg/dl) was analyzed by plotting the reciprocal of serum creatinine versus time in days before and after stenting.
Results: All pts had deterioration of renal function prior to intervention. At 47.4 ± 31.2 months post intervention renal function improved or did not change in 76% and worsened in 24% of NDM patients compared to 73% and 27% of DM pts respectively (p=NS).(fig)



Renal function over time.

Conclusion: Renal artery stenting is equally beneficial in DM and NDM pts with impaired renal function and atherosclerotic renal artery stenosis.

P578 Immediate and follow-up results of carotid artery stenting with cerebral protection: a single centre experience on 100 consecutive procedures

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Background: Purpose of this prospective study was to determine periprocedural complications and short- and medium-term outcomes in a cohort of patients treated with carotid stent implantation routinely using cerebral protection devices.
Methods and Results: Stent implantation was attempted in 96 consecutive patients (mean age 70,8±14 years; 77,1% males) presenting significant stenosis (>70%; mean 82,8±9%) in 100 lesions of the extracranial carotid artery. Forty lesions (40%) presented previous stroke or transient ischemic attacks related to the ipsilateral hemisphere. Cerebral protection was performed using filter devices in 93% of procedures and endoluminal clamping of the common and external carotid artery in 5% of procedures. In 2 procedures it was not possible to deploy a protection device. Selfexpandable stents (mesh-wire 60%; nitinol 40%) were successfully implanted in all lesions. Neurological complications during the procedure and in-hospital, occurred after 3 procedures (3%). These were 1 major stroke (1% amaurosis of ipsilateral eye) and 2 transient ischemic attacks (2%). During a follow-up of 9.3 ±3.5 months (mimum 3 months) further neurologic events did not occur. Ecocolor-Doppler at 6month after the procedure was available in 78 treated lesions and >50% in-stent restenosis was found in 2 lesions (2.5%). Major adverse cardiac events during follow-up occurred in 2 patients (2%), this were 1 fatal an 1 non-fatal myocardial infarction.
Conclusions: Incidence of procedural complication during carotid artery stenting with routine use of cerebral protection appeared low. During follow-up no further neurological events occurred and restenosis rate was low.

P579 Carotid artery stenting in patients at high clinical risk of carotid endarterectomy complications: immediate and long-term outcome

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Background: Carotid endoarterectomy (CEA) has been shown to be superior to medical treatment in reducing the overall risk of stroke in patients with symptomatic (>50%) or asymptomatic (>60%) carotid artery stenosis compared to medical treatment. Nevertheless, in subgroups of patients at high risk of acute events, a high complication rate may limit the efficacy and safety of this approach. The aim of this study is to evaluate the efficacy and safety of the percutaneous approach to carotid artery stenosis in a subgroup of patients at higher risk of CEA complications.
Methods: Between May 1998 and January 2002 161 patients (164 lesions) with elective indication and a Mayo Clinic Risk Score > 2 underwent percutaneous carotid revascularization at our institutions. Transient Ischemic Attack (TIA), minor stroke and major stroke were classified accordingly to The National Institutes of Health Stroke Scale (NIHSS). The incidence of death, acute neurological events and myocardial infarction was assessed in-hospital and during follow-up.
Results: 88% of patients were in Mayo clinic risk stratification grade III, 5% in grade IV, 7% in grade VI. Angiographic success was 97.5%; four lesions could not be treated due to severe vessel tortuosity. Procedural success was obtained in 96.2% of patients. Mean residual diameter stenosis was 4.7±5.2 mm. Distal protection device was used in 79.5% of the lesions and stenting was performed in all the treated lesions except for three (in-stent restenosis). Debris was founded in 40% of the protection devices. In-hospital events consisted of 10 (6.2%) TIAs, 1(0.6%) category 1 minor stroke and 1(0.6%) major stroke. At follow-up (mean time:10±5.6 months) death occurred in 9(5.6%) patients; in two of them (1.2%) it was related to acute neurological events, in the remaining 7 (4.4%) it was related to cardiac events (4 patients) and other causes (3 patients). Severe restenosis occurred in 3 (1.8%) lesions.
Conclusions: Carotid artery stenting is feasible and can be performed with extremely low rate of acute events in patients at high clinical risk of CEA complications. The positive results are maintained on long-term outcome with a low incidence of neurological acute events and a low rate of restenosis.

P580 Arterial stiffness is associated with atherosclerotic plaques but not with intima-media thickness in healthy middle-aged subjects

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The relationship of arterial stiffness with atherosclerosis is controversial and has been scarcely studied in large population-based samples, particularly in youngest subjects. In a sample of middle-aged apparently healthy subjects, we studied the relationships of carotid-femoral pulse wave velocity (PWV) with the presence of atherosclerotic plaques on the one hand and with common carotid intima-media thickness (IMT) on the other hand.

Methods: A sample of 905 southwestern French men and women (35 to 64 years), taking part in the Third French MONICA cross-sectional Survey on cardiovascular risk factors (1994-1996) was analyzed. Each participant filled in extensive questionnaires focused on their cardiovascular risk factors and a blood sample was drawn for biological measurements. Heart rate, arterial blood pressure and carotid-femoral PWV were measured in supine position. PWV measurements were performed with a semi-automatic device (Complior). B-mode ultrasonography was used to measure common carotid IMT and to assess the presence of atherosclerotic plaques in common, internal and external carotid and femoral arteries.

Results: Mean values of PWV and IMT were 9.0 m/s (standard error: 0.06) and 0.59 mm (0.003) respectively and the proportion of subjects with at least one plaque was 50.4%. There was a significant increase in PWV values according to the number of plaques in the artery explored sites: mean PWV equaled 8.6 (0.06), 9.3 (0.11), 10.4 (0.19) and 11.4 (0.45) m/s respectively in subjects with 0 to 1; 2 to 3; 4 to 5; and 6 plaques or more ($p<0.0001$). A similar trend was observed with common carotid IMT quartiles: mean PWV values were 8.3 (0.11), 8.8 (0.11), 9.1 (0.11) and 9.6 (0.11) m/s respectively in the first, second, third and fourth quartiles ($p<0.0001$). After adjustment for sex, age, tobacco consumption, body mass index, resting heart rate, systolic blood pressure, total and HDL-cholesterol and glycaemia, PWV remained significantly associated with the presence of plaques: adjusted means were 8.8 (0.06), 9.0 (0.10), 9.5 (0.17) and 10.0 (0.40) m/s in subjects with 0 to 1; 2 to 3; 4 to 5; and 6 plaques or more (p for trend: $p<0.001$). However, after adjustment, the relationship between mean values of PWV and IMT quartiles disappeared (adjusted p value for trend: $p=0.42$).

Conclusion: In this sample, PWV was independently associated with atherosclerotic plaques but not with common carotid IMT, perhaps because of the relatively low values of IMT observed in this sample of middle-aged subjects.

P581 Folic acid enhances endothelial function and reduces blood pressure in smokers: a randomised controlled trial

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Objective: Chronic cigarette smoking is associated with increased plasma homocysteine concentrations, endothelial dysfunction, and arterial stiffening. Homocysteine per se induces endothelial dysfunction and arterial stiffening and might account, at least partly, for the vascular abnormalities observed in smokers. The aim of the study was to determine whether folic acid supplementation, by reducing plasma homocysteine concentrations, enhanced endothelial function and reduced arterial stiffness in smokers.

Methods: Twenty-four healthy cigarette smokers (age 37.8±2.5 years, mean±SEM) were randomly assigned to 4-week folic acid 5 mg/d or placebo. The following were measured before and after treatment: 1) peripheral vasoreactivity (forearm arterial blood flow, FABF) during intra-arterial administration of endothelium-dependent (acethylcholine 1.5, 4.5, and 15 μg/100ml/min) and endothelium-independent (sodium nitroprusside 1, 2, and 4 μg/100ml/min) vasodilators; 2) carotid-femoral pulse-wave velocity (PWV); 3) blood pressure (BP).

Results: Folic acid reduced homocysteine concentrations (10.8±0.6 vs. 8.2±0.5 μmol/L, $p<0.001$) and enhanced endothelium-dependent vasodilatation during each acetylcholine infusion rate (FABF ratio between the infused and control arm at baseline 1.09±0.03 vs. 1.41±0.09 after treatment, $p<0.01$; 1.39±0.07 vs. 1.83±0.12, $p<0.01$; 1.65±0.16 vs. 2.72±0.36, $p<0.05$) whilst endothelium-independent vasodilatation was unaffected. A significant fall in BP was also observed (mean BP 88±2 vs. 83±1 mmHg, $p<0.01$). By contrast, PWV did not change (8.4±0.3 vs. 7.8±0.4 m/s). No changes in homocysteine concentrations, FABF, BP, and PWV were observed in the placebo group.

Conclusions: Short-term folic acid supplementation significantly enhanced endothelial function and reduced blood pressure in young chronic smokers. Thus, a simple, non-toxic, and relatively inexpensive vitamin intervention might be a useful primary cardiovascular prevention tool in this high-risk group.

P582 Predictive value of intima-media thickening and asymptomatic carotid plaque for cardiovascular events in the follow-up

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During the years 1998-1993, on behalf of the research project CIFTI 4-GESCO-MUTST, we examined 755 subjects of both gender, aged between 18 and 85 years, without or with risk factors, to evaluate the prevalence of asymptomatic carotid lesions (IMT= intima-media thickening and ACP= asymptomatic carotid plaque). In this study we demonstrated that these lesions are more frequent in the male gender, increase with aging and are significantly related with the presence of single RF (arterial hypertension, diabetes mellitus, hypercholesterolemia, smoking) as well as with multiple and associated RF. The follow-up of these subjects continued and in this moment we have available data of 5 years follow-up concerning 123 patients, 42 normal, with mean age of 56.84± 13.96 years, 39 with IMT and mean age of 63.18± 13.21 and 42 with ACP and mean age of 69.62± 6.98 years, at first examination. The mean number of RF was 1.36± 1.18, 1.77± 1.20 and 1.76± 1.3 respectively in the three groups. In the group of normal subjects 38.09% remained normal, 21.42% showed an evolution versus IMT and 28.57% versus ACP, while 11.9% died. In the group with IMT, 7.69% showed a regression, 48.71% were unchanged, 20.51% died and only 2.56% had non-fatal events. In the group with ACP only 2% showed a partial regression of lesions, 40.7% remained unchanged, 45.23% died, while 11.90% had non-fatal evens. Distinguishing between cardiovascular and non cardiovascular death, the frequency was respectively 0.47 and 1.9% for year in normals, 2.56% and 1.53% for year in patients with IMT and 3.33% and 4.76% for year in subjects with ACP was. 7 fatal AMI were registered in the group with ACP and 1 in the group of normals, 3 non fatal AMI in the group with ACP, 5 fatal stroke in the group with ACP, 2 non fatal stroke in the group with ACP and 1 in the group with IMT.

The preliminary results of our study referring to a 5 years follow-up of 123 subjects, shows that the most part of patients with asymptomatic carotid lesions have a progression of lesions as well as an important increase of both total mortality and cerebrovascular and cardiac, fatal and non fatal evens.

So, our study suggests that asymptomatic carotid lesions have to be considered an important risk factor for cardiovascular morbidity and mortality.

P583 Coronary ectasia and varicose veins; is there any relationship?

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Coronary artery ectasia (CAE) represents abnormal coronary arterial dilatation, the diameter of which exceeds by 1.5 times the adjacent normal segment. It is estimated that CAE affects about 2% of the general population and it is found in 1.4-4.9% of coronary arteriograms. The aetiology of CAE remains unknown and its origin is not clear whether it is a pure wall defect, a pure endothelium defect or a mixture of these. The same helds true in varicose veins (VV), a common clinical situation, with a prevalence of 15-30% in all populations. Though CAE and VV refer to the pathology of different vessels, the underlying histologic changes of the arterial wall between the two entities show some interesting similarities. We sought to assess the prevalence of VV in patients with CAE. From previous studies performed in our geographical area, the prenalence of VV in the general population was found to be about 23%.

Methods: During the last two years, all pts undergoing coronary arteriography in whom CAE was present, were immediately checked clinically for the presence of VV. Another 165 subjects without profound disease were also examined for the presence of VV during the same time period.

Results: A total of 6768 pts underwent coronary arteriography at our institution within 2 years. CAE was present in 147 of them (2.17%). Fifty-nine pts with CAE were found to suffer from VV (40.13%), and were significantly more than the 41 of the 165 control subjects (24.85%) in whom VV were present, $p<0.001$ (table).

	Varicose Veins (VV)	Lack of VV
Coronary Artery Ectasia (N=147)	59 (40.13%)	88 (59.87%) °
General Population (N=165)	41 (24.84%)	124 (75.16%) °

° $P<0.001$

Conclusions: It seems that there is a relationship between CAE and VV, as VV are more common in pts with CAE. While there are important difficulties in studying the pathology of both CAE and VV in the same patient at the same time, an underlying generalized defect of the vessel wall might be responsible for such an observation and merits further study.

P584 Long-term follow-up of critical limb ischaemia (CLI) treated by spinal cord stimulation

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Introduction: Although Spinal Cord Stimulation (SCS) has been effectively used for unrecontructable CLI, during the past 10 years, in controlled studies, for some clinical investigators (TASC 2000) SCS "on current evidence cannot be recommended in the treatment of CLI".
Aim of the study: A. Evaluation of the clinical response to SCS treatment in long-term follow-up. B.Evaluation of the transcutaneous oxygen and carbon dioxide pressures -TCpO2 and TCpCO2-, LaserDoppler Flowmetry -LDF- to define local microcirculatory variations and the predicting capacity in limb salvage. **Subjects and methods:** 11 consecutive CLI patients, 3 in stage III, 8 in stage IV (M/F: 7/4, mean age 71.8,5 diabetics), with unrecontructable CLI, were treated for a minimum of 15 days with a temporary SCS and then with a permanent spinal pacemaker. The patients were subject to clinical (analgesic therapy, trophic lesions and walking capacity) and instrumental evaluation by means of the measurement of cardiac frequency (CF) and arterial pressure (AP), Winsor index (WI), TcpO2 and TCpCO2, LDF: these evaluations were made both prior to SCS treatment and in the SCS follow-up of 15, 90, 180, 360, 730 days. RESULTS: the overall mortality rate was 27% and the overall amputation rate was 9%. At the clinical level 73% of cases were Responders (n=8)vs 27% Non-responder (n=3;1 amputation within 6 months). No significant variations in CF, AP and WI were registered. However, TCpO2 of the symptomatic foot of the Responders showed notable mean pressure improvement ($p<0.03$) from zero to 30 mmHg after 15 days and to 40 mmHg after one year of stimulation. In non-Responders the TCpO2 remained consistently below 5 mmHg for the entire duration of the treatment. SCS did not affect the high TcpCO2 basal median in the Non Responders, while in the Responders the TcpCO2 (m: 49mmHg) values normalised within a maximum of three months (<40 mmHg). In the Non Responders, the LDF confirmed low levels of perfusion, lack of an increase in the LDF signal after maximal heating, and marked alteration in the postural venous-arterial reflex (VAR) both at the hallux and at the first inter-metatarsus, while the Doppler laser signal indicated more favourable results in the Responders.
Conclusions: This study confirms the indication of SCS in patients in CLI who are no longer susceptive to medical therapy and/or surgery. The instrumental evaluation is more accurate than clinical evaluation.TcpO2 and TcpCO2 continue to be the most useful predicatibility index in patients subject to the permanent implant of a medullary pacemaker.

P585 Significant association between markers of systemic inflammation and the extent of atherosclerosis in the arterial vessel tree

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Inflammation in the arterial vessel wall has been considered to play an important role in the pathogenesis of atherosclerosis. Recent prospective studies have shown that cytocines like interleukin-6 (IL-6) or tumor necrosis factor a (TNF a) as well as acute phase proteins like sensitive C reactive protein (CRP) or fibrinogen are associated with atherosclerosis. Therefore we evaluated the correlation between different markers of inflammation and the extent of atherosclerosis including coronary, carotid and peripheral arteries.
Methods: In a prospective study we included 825 patients (70% men, mean age 63 years) preceding heart catheterization. The extent of atherosclerosis was determined by coronary angiography (stenosis >30%), carotid duplex sonography (stenosis >50%) and by evaluation of the ankle-arm index (= ankle/arm blood pressure, pathologic <0.9). Patients were divided into 3 groups with regard to the extent of atherosclerosis to: control (=no atherosclerosis, N=91), limited disease (=atherosclerosis in 1 vascular region, N=394) and advanced disease (=atherosclerosis in 2 or 3 vascular regions, N=340). Blood samples were taken by all patients and values of IL-6, TNF a, CRP and fibrinogen were evaluated. Regression test was used for statistical evaluation.
Results: Median (25th-75th percentile) inflammatory parameters in the 3 patient groups are shown in the table.

Inflammation and atherosclerosis

	Control	Limited disease	Advanced disease	
IL-6 (ng/ml)	8.2 (4-13)	11.0 (5-23)	11.9 (6-24)	P<0.002
TNF a (pg/ml)	22.2 (16-27)	22.9 (16-29)	24.3 (17-32)	P<0.02
CRP (mg/L)	2.6 (1-7)	4.3 (2-11)	5.0 (2-15)	P<0.0001
Fibrinogen (mg/dl)	294.0 (257-330)	328.5 (279-397)	354.0 (290-434)	P<0.0001

Association between inflammatory parameters and extent of atherosclerosis.

Conclusion: There was a significant correlation between all evaluated markers of systemic inflammation and the extent of atherosclerosis including coronary, carotid and peripheral vessels.

P586 Nebivolol restores vasomotion and vasodilator capacity of microcirculatory bed in hypertensive patients with altered microvascular function

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Nebivolol is a beta1-adrenergic blocker suggested to improve NO-dependent vasorelaxation in the forearm model in human hypertension. The so-called low frequency flowmotion waves (LF) of peripheral microcirculation, i.e. the low frequency components (0.05- 0.1 Hz) of the oscillatory Laser Doppler perfusion monitoring (LDPM) signals, are related to spontaneous arterial vasomotion and depend at least partially on endothelial functional integrity. These frequency components usually disappear in presence of severe systemic vascular disease.
Aim of the study was to assess the effects of Nebivolol therapy on peripheral microcirculation in patients (pts) with essential hypertension (HBP). Methods: in 22 HBP pts (mean age 52±10, 14 males, SBP/DBP 151±9/98±7 mmHg) and 20 age and gender matched NT(SBP/DBP 118±12/72±9 mmHg), forearm skin blood flow was assessed by LDPM at rest and after stepwise doses of Acetylcholine (ACh) and Sodium Nitroprusside (SNP) administered simultaneously by iontophoresis at the two forearms. Oscillatory components of LDPM were assessed by time-dependent power spectrum analysis of the resting signals. In HBP the study was repeated after Nebivolol therapy (21 days, at 5 mg/die).
Results: In HBP pts, peak response to ACh was comparable to NT (peak ACh: 50±29 vs 63±24 PU p=ns) while peak response to SNP was significantly lower (peak SNP: 34±24 vs 54±35 PU, $p<0.05$). However, comparing pre-treatment dose-response curves to ACh and SNP in HBP pts to the average of NT, we could distinguish two subgroups: A) with a depressed response (flow max<1sd below the average peak flow in NT, n=9) and B) with a preserved response (flow max>1sd below the average peak flow in NT, n= 13). Before therapy, LF were detected in 8/22 pts (3 A and 5 B) and in all NT. After therapy, BP significantly decreased in all pts (average 134±12/81±10 mmHg, $p<0.001$ vs baseline). Flow response to both vasoactive agents did not significantly change compared to pretreatment value in the overall population (maximal response to ACh: 51±15 PU, and SNP: 46±30 PU, p=ns vs pretreatment). However, the response to ACh and SNP significantly improved ($p<0.05$) in those pts with a corresponding basally impaired response. In LDPM signals, LF were detected in 9 more pts (4 A and 5B) as compared to pretreatment recordings ($p<0.05$).
Conclusions: in HBP, Nebivolol treatment improves both arteriolar vasomotion and vasodilator capacity at peripheral microcirculatory level. The enhancement of the vasodilator response to ACh and SNP appears to be selective in those pts with basally impaired vascular function.

P587 Effects of gender on large artery elasticity. A study in male to female transsexuals

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It is not well determined whether the gender differences on cardiovascular disease may be explained, at least partially, by differences on large artery elasticity. Also, limited information exists regarding vascular function in male to female transsexuals.
Methods: Towards this end, we evaluated aortic elastic properties in 13 male to female transsexuals (age 44±9 years, 18±11 years after surgery) and we compared these findings with those observed in 10 premenopausal women (age 42±5 years) and in 10 men (age 43±5 years). Aortic compliance was evaluated non-invasively on the basis of Doppler ultrasound measurements of pulse wave velocity (PWV) from the carotid to femoral artery by the foot-to-foot method. All included subjects had a negative glucose intolerance test.
Results: The three groups of men, women and male to female transsexuals were matched for age (44 vs 42 vs 43 years, respectively) body mass index (25 vs 23 vs 24 Kgr/m^2, respectively), smoking status (current smokers 45% vs 42% vs 48%, respectively), total cholesterol plasma levels (232 vs 229 vs 218 mg/dl, respectively) and office blood pressure (115/75 vs 110/75 vs 115/73 mmHg, respectively) (p=NS for all the above cases). Also, these three groups did not differ regarding the left ventricular echocardiographic data of left ventricular mass (171 vs 142 vs 158 gr, respectively), and relative wall thickness (0.41 vs 0.42 vs 0.41, respectively)(p=NS for all measurements). In contrast, the aortic PWV was significantly higher in men compared to transsexuals and women (217±30 vs 204±21 vs 201±20 cm/sec, respectively) while the PWV did not differ between transsexuals and women (p=NS). In the entire population aortic PWV had a positive correlation with age ($r=0.30$, $p<0.05$), systolic BP ($r=0.44$, $p<0.005$)
Conclusion: These results suggest that vascular adaptations in male to female transsexuals are more closely related to those observed in premenopausal women than those in age-matched men.

P588 Agonistic antibodies against the angiotensin-1 receptor from preeclamptic patients stimulate the NADPH oxidase

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We recently identified agonistic autoantibodies directed against the angiotensin AT1 receptor (AT1-AA) in the plasma of preeclamptic women. To elucidate whether or not AT1-AA could account for some of the clinical findings, we studied the effects of AT1-AA on reactive oxygen species (ROS) production, NADPH oxidase expression, and NF-kB activation in vascular smooth muscle cells (VSMC) and human primary trophoblasts. Antisense against p22 phox reduced AT1-AA induced ROS activation. Ang II and AT1-AA increased ROS production, as well as the expression of the NADPH oxidase components, p22, p47, and p67 phox, in western blot. We next tested whether or not AT1-AA could lead to nuclear factor-kB activation in VSMC and trophoblasts. We used electrophoretic mobility shift assays and found that AT1-AA activated NF-kB. IkBalpha expression was reduced in response to AT1-AA. VSMC from p47 Knockout mice showed reduced NF-kB activation in response to AT1-AA. Furthermore, p22, p47, and p67 phox expression in the placentas from preeclamptic patients was increased, compared to normal placentas. Increased ROS production was observed in preeclamptic placentas in situ. Correspondingly, we observed that NF-kB was activated and IkBalpha reduced in placentas from preeclamptic women, compared to normal placentas. Thus, NADPH oxidase is potentially an important source of ROS and upregulates NF-kB in preeclampsia. We suggest that AT1-AA via activation of the NADPH oxidase could account for the well-established production of ROS and chronic inflammatory responses in preeclampsia.

P589 Dialytic membrane biocompatibility on the development of atherosclerosis in haemodialysis: the role of chronic infections

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Haemodialytic treatment is often associated with an increased cardiovascular mortality and morbidity due to a complex inflammatory process that accelerates atherosclerosis.Chronic low-grade infections with Chlamydia pneumoniae (CP) or Helicobacter pylori (HP) may play a pathogenic role in the development of atherosclerosis (ATS). The aim of this study was to investigate the relationship between different types of dialytic membranes, seropositivity to CP or HP and early markers of ATS. The study was carried out in 68 patients (M 39 F 29; mean age 54, range 18-70 years; mean time on dialysis 50 months) on renal replacement therapy for over 6 months with cellulosic (C) (32) or synthetic (S) (36) membranes. In this patients we evaluated anti-CP and anti-HP IgG titres, C reactive protein (CRP) levels, serum albumin, PTH, chol and plasma C5b-9 concentrations,intima-media thickness (IMT) and number of ATS plaques in carotid arteries (PL) obtained by high resolution vascular echography. The concentrations of CRP were directly and significantly correlated with the IMT ($r2=0.56$, $p<0.001$). No correlation could be observed between these parameters and serum PTH and chol concentrations, but instead, was interesting to observe that patients treated with C membranes as compared to patients treated with S membranes presented higher CRP (C 0.66±0.6, S 0.24±0.2 mg/dl) and C5b-9 (C 187±82, S 136±33 ng/ml) levels and an increased IMT (C 1.08±0.3, S 1.01±0.2 mm). On the other hand, patients with an anti-CP IgG titre higher than 1:8 presented a significantly higher IMT, number of PL, and presented an higher CRP concentration(table). No differences were observed in either IMT or number of PL in patients with (titre higher than 1:4) or without anti-HP IgG.

	IMT	PL	CRP
anti-CP > 1:8	1.03 ± 0.26	0.55 ± 0.3	0.53 ± 0.51
anti-CP < 1:8	0.86 ± 0.13	0.12 ± 0.2	0.20 ± 0.15
p	< 0.005	< 0.002	< 0.05

anti-CP: antibodies anti C. pneumoniae (titre); IMT: intima-media thickness carotid arteries (mm); PL: atherosclerotic plaques >40% (n°); CRP: serum levels of C reactive protein (mg/dl)

In conclusion, our data would suggest that persistent CP, but not HP; infection as well as the use of cellulosic membranes may play a key role in the development of ATS lesions

P590 Decreased endothelial eNOS expression in varicose veins is associated with increased smooth muscle cell apoptosis

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Introduction: The pathogenesis of varicose veins (VV) is poorly understood. VV are characterized by thinning of the medial layer through loss of medial smooth muscle cells. We previously identified the loss of VV-endothelial eNOS expression and function as a key feature of the pathology of VV. Because inhibition of NO synthesis increases apoptotic cell death, those segments of saphenous veins that had been investigated for their NOS expression status, were subjected to TUNEL analysis. Furthermore, genomic DNA from those same patients were analyzed for a candidate eNOS polymorphism to understand whether the observation was a primary genetic defect, or a secondary, observational finding.

Material and Methods: We studied specimens from 33 patients (19f/14m) undergoing VV excisions and from 28 (13f/15m) controls. NOS activity was measured in saphenous veins endothelial scrapings by the conversion of L-[14C]arginine to L-[14C]citrulline in pmol/min/g. In situ labeling of DNA fragments by TUNEL was performed with the ApopTag in situ apoptosis detection kit. Apoptotic indices were determined by dividing the number of TUNEL-positive cell nuclei by the total number of cell nuclei/100. Finally, genomic DNA was amplified using oligonucleotide primers specific for intron 4 of eNOS.

Results: In accord with the immunohistochemical finding of a dramatically reduced endothelial eNOS expression, endothelial eNOS activity was significantly lower in VV compared with controls (p=0,03, table). In addition, intimal and medial apoptotic indices were significantly increased in VV (p=0,028 and 0,0006, respectively). Genetic analysis revealed that the allelic frequency of NOS3 T-788C was not different from a reference population.

	INTIMA		MEDIA	
	Healthy vein	Varicose vein	Healthy vein	Varicose vein
Apoptotic Index	0.14±0.06	0.23±0.12	0.15±0.1	0.28±0.1
eNOS-activity	968.2±1025	138.3±109	not applicable	not applicable

Discussion: This study suggests that the lack of eNOS expression in VV endothelium is associated with enhanced smooth muscle cell apoptosis, thus contributing to progressive intimal and medial fibrosis. However, the NOS3 T-788C polymorphism is not a key mutation underlying eNOS loss from VV endothelium.

P591 Invasive and non-invasive evaluation of spontaneous arteriogenesis in a novel porcine model for peripheral arterial obstructive disease

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Introduction: Most experimental arteriogenesis data are based on studies using small animals such as mice or rabbits, which only partially reflect the situation in humans with peripheral artery obstructive disease (PAOD), because of the relatively small tissue mass necessary for the morphogenesis of new arteries in mice versus man. The objective of this study was to evaluate a pig hindlimb ligation model for PAOD.

Methods: 12 farm pigs (FP) and 13 Göttinger minipigs (MP) underwent a ligation of the A. Femoralis Superficialis, distal to the bifurcation of the A. Femoralis Profunda. The animals were examined either directly after ligation (FP; n=7 and MP; n=4) or after two weeks of intra-arterial PBS infusion (FP; n=5 and MP; n=9). In the terminal experiment, inflow to the legs was assessed using ultrasonic flow probes placed on the A. Iliaca. Distal arterial pressures in the legs as well as perfusion pressure in the abdominal aorta were measured using fluid-filled catheters before and after installation of an extracorporal system in the abdominal aorta. Using this pump driven extracorporal circulation, leg perfusion pressures could be controlled. At different perfusion pressure levels and under maximal vasodilatation using papaverin, inflow to the legs and distal pressures were assessed and vascular conductance was calculated. X-ray & MR angiographies and histology were performed in some animals to visualize collateral arteries.

Results: Peripheral arterial pressures and flow in the A. Iliaca dropped markedly after acute ligation in both farm pigs (from 94±9 to 25±9 mmHg and 189±29 to 101±24 ml/min) and minipigs (from 71±18 to 34±7 mmHg and 91±30 to 29±17 ml/min). Pressure and flow recovered partially after two weeks in FP and MP (61±9 and 55±12 mmHg and 158±25 and 64±36 ml/min, respectively). Conductance increased from 4% and 9% of the normal leg in MP and FP after acute ligation, respectively, to 9% in minipigs compared to 22% in farm pigs after two weeks ($p<0.05$). MR and X-ray angiography showed collateral artery formation from the A. Femoralis Profunda.

Conclusions: This is the first pig model for hemodynamic assessment of growth of collateral arteries in the peripheral circulation, that is suitable for evaluation of arteriogenic effects of growth factors or genes. Age and animal strain may have an impact on this collateral vascular development.

P592 Is there a scientific rationale for routine greater saphenous vein stripping?

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Background: The stripping of the entire Greater Saphenous Vein (GSV) is currently the most used surgical procedure performed in patients with varicose veins, based on the assumption that, in these patients, all superficial veins, including the entire GSVs, are heavily affected by the varicose disease. Using recently validated well defined echographic criteria, we assessed, in a large series of patients, the extent of varicose involvement of the entire GSV.
Methods: We performed echo-Doppler examination in 350 lower limbs with primary varicose veins in the territory of the GSV due to incompetence of the sapheno-femoral junction, belonging to 300 consecutive patients. Patient population consisted of 71 males and 229 females, age-ranging 21 to 84 years. A varicose vein was defined as a diffusely swollen and elongated vein with bends, and a segmental swelling was defined as a length-limited venous dilatations less than 2.5 cm long. Valve incompetence was diagnosed by detecting a retrograde flowusing both compression/release test and the Valsalva maneuver.
Results: By the above mentioned criteria, only 1 GSV out of 350 was varicose, and 82 GSVs out of 350 showed segmental swellings. Fifty-two percent of the examined GSVs were competent for at least half of their total length and only 7% were completely incompetent.
Conclusions: Our findings show that the GSV is largely spared by the varicose disease in the majority of cases. Accordingly, there appears to be no scientific rationale for routine Greater Saphenous Vein stripping.

P593 Late acute thrombotic occlusion after endovascular brachytherapy and stenting of femoro-popliteal arteries

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Introduction: Endovascular brachytherapy (EVBT) has been proposed as a promising treatment modality to reduce restenosis after angioplasty. However, the phenomenon of late acute thrombotic occlusion (LATO) in patients receiving EVBT after stenting is of major concern. Aim of this article is to underline the importance of this complication after EVBT and intravascular stenting of the femoro-popliteal arteries occurring in a running randomized trial.
Methods and results: A total of 294 patients have been randomized so far in a running prospective multicenter trial of patients undergoing EVBT (Ir 192; 14 Gy in 5mm) after percutaneous recanalisation of femoro-popliteal obstructions. Ninety-four patients out of 204 patients, who completed the 6-month follow-up, were randomized to EVBT.
LATO occurred exclusively in 6/22 patients (27%) receiving EVBT after intravascular stenting and in concomitance with reduction of antithrombotic drug prevention (Clopidogrel). Conversely, none of the 72 patients undergoing EVBT after balloon angioplasty without stenting ($p<0,01$), and none of the 110 patients without EVBT presented LATO ($p<0,05$).
Conclusion: Late thrombotic occlusion occurs not only in patients undergoing EVBT after percutaneous coronary recanalisation but also after stenting of the femoro-popliteal arteries and may challenge the benefits of endovascular radiation. The fact that all our cases with LATO occurred in concomitance with stopping Clopidogrel may indicate a possible rebound mechanism. An intensive and prolonged antithrombotic prevention is probably indicated in these patients.

P594 Aortic atherosclerotic disease as a risk factor for cerebrovascular accidents in patients without prior cerebrovascular events

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Background: Atherosclerotic disease of the ascending aorta and the aortic arch (detected by transesophageal echocardiography) is known as a significant predictor of recurrent brain infarction and other vascular events in patients with prior cerebrovascular accidents. After a literature review we found little evidence about aortic atherosclerosis as a cerebrovascular risk factor for patients without a prior cerebrovascular event.
Aim: To evaluate the frequence and prognostic value of aortic atheromas detected by transesophageal echocardiography in these patients.
Methods: We studied 414 consecutive patients who performed a transesophageal echocardiography between January 1999 and July 2001. Baseline clinical characteristics (including coronary risk factors, presence of atrial fibrillation, carotid stenosis and peripheral arterial disease) were recorded. At transesophageal echocardiography we studied atherosclerotic aortic plaques morphology giving a grading from I to V (grade I. minimal intimal thickening, grade II: extensive intimal thickening, grade III: sessile atheroma, grade IV: protruding atheroma, grade V: mobile atheroma).
Results: We found aortic atheromas in 77 cases (19,3%, mean age 66,0 ± 9,6 years, male/femal ratio= 46/31). Aortic atheromas were found in ascending aorta in 22 cases (28,6%), in the aortic arch in 37 cases (48,1%) and in the descending aorta in 18 cases (23,3%). Aortic plaque grading was: grade I in 17 cases (22,0%), grade II in 28 cases (36,4%), grade III in 11 cases (14,3%), grade IV in 14 cases (18,2%) and grade V in 7 cases (9,1%). After a mean follow-up of 29,2 months (range 6-48 months) we observed 33 vascular events (42,9% of all case: 24 cerebral infarction, 6 transient ischemic attacks, 3 myocardial infarction). A higher number of vascular events were recorded in patients with aortic plaques grade III vs grade I-II (respectively 81,2% vs 11,1%, $p<0,001$) and grade IV-V vs grade I-II (respectively 90,5 vs 11,1%, $p<0,001$). After adjustment for the presence of carotid stenosis, atrial fibrillation, peripheral arterial disease and coronary risk factors we found that only grade IV-V (OR 5,12 CI 95% 1,78 to 8,4) was an independent predictor of cerebrovascular events.
Conclusions: Asymptomatic atherosclerotic aortic disease can be a frequent occasional finding at transesophageal echocardiography. Presence of high risk plaques by grading I to V is a significant predictor of cerebrovascular events also in asymptomatic patients without prior cerebrovascular events.

P595 Predictive value of atherosclerotic risk factors, chest X-ray, haemostatic and inflammatory parameters for aortic arch atheromatosis

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Aortic arch atheromatosis (AAA) is a common cause of cerebral and peripheral embolisations. Transesophageal echocardiography (TEE) is the diagnostic method of choice showing not only the extension and consistency of aortic atherosclerotic plaques but also the mobility of superimposed thrombi. In most cases AAA is only detected when the first embolic event has already occurred. This study was therefore designed to identify predictive factors for AAA.
112 consecutive patients on routine TEE entered the study. Exclusion criteria were warfarin therapy, recent surgery, any sign of infectious, immunological or malignant disease. Among classic atherosclerotic risk factors diabetes mellitus was accompanied with the highest risk for AAA Grade IIIa and IIIb (odds ratio 3.0), followed by hyperlipidemia (2.5) and arterial hypertension (2.3). Age above 70 years was accompanied by a 1.8-fold increased risk. Patients with calcifications of the aortic shadow on standard chest x-ray had a 4.6-fold higher prevalence of AAA. Patients with AAA grade IIIb had significantly higher levels of C-reactive protein (19.9 vs. 7.9 mg/l), prothrombin fragments F1+2 (1.21±0.70 vs. 0.90±0.65 nmol/l), PAP (727±298 vs. 440±212 µg/l) and D-dimers (968±656 vs. 452±310 µg/l), but lower ATIII (92.0±18.0 vs. 99.6±20.1%). Patients with echolucent plaques in contrast to other plaque morphologies were older (70.3±7.8 vs. 65.4±9.5) and showed significantly higher leves of von Willebrand factor antigen (148.0±46.0 vs. 126.4±32.1%), D-dimers (920±569 vs. 406±312 µg/l) and PAP (623±288 vs. 454±237 µg/l). AAA is accompanied by an elevation of inflammatory and hemostatic parameters, while patients with classic cardiovascular risk factors display a higher prevalence of this disease. Further prospective studies will have to establish a risc score that identifies patients that might profit from a TEE screening.

P596 Evolution of intramural haematoma to aortic aneurysm

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Aortic intramural haematoma (IMH) evolves in the short-term to dissection, rupture or reabsorption. Long-term evolution of IMH remains relatively unknown. From January 1991 to December 2000, 68 patients with acute aortic syndrome were diagnosed of IMH. Of these, 48 (67±8 y) were treated medically and followed on an out-patient basis (5-261 months; 57±53). TEE, CT and MRI were performed at 3 and 6 months and annually thereafter. 3 patients underwent endovascular treatment and two surgery (>24 months).
In the mid-term (6 months), IMH was almost totally reabsorbed in 15 (33%), had evolved to classical dissection in 5 (11%) or localized dissection in 15 (33%).
In the long-term, normal aorta (without dilation) was observed in 15 (33%), classical dissection in 5 (11%), and saccular or fusiforme aneurysm in 16 (35%) and 10 (22%), respectively.
Predictive variables of IMH reabsortion were basal aortic diameter at the IMH site (46±1.2 vs 39±1.1 mm, $p<0.001$) and IMH thickening (14±0.7 vs 12±1 mm, $p<0.04$).
12 of 16 (75%) saccular aneurysms had evolved in short-mid-term with localized dissection ($p<0.001$). Aneurysms formation had greater diameters in acute phase and IMH thickening than the remaining patients (47±1.4 vs 40±1.2 mm, $p<0.001$) and (14±0.7 vs 11±0.9 mm, $p<0.01$), respectively.
Conclusion: Most IMH evolved to normalcy or aneurysm formation after 6 months of follow-up. Aortic diameter, IMH thickening and localized dissection in the short term have prognostic value for posterior aneurysm formation.

P597 Weight loss after bariatric surgery normalizes aortic distensibility and left ventricular mass in morbidly obese subjects. Six months follow-up

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Mordid obesity has been associated with a high incidence of heart failure. Aortic distensibility (AoD) is an important determinant of left ventricular (LV) function. We investigated whether: a) increased body mass index (BMI) is related with impaired AoD and LV mass b) weight loss after bariartic surgery (gastric bypass) is related with changes in lipids, glucose serum levels and resting blood pressure in parallel to improvement of AoD and LV mass in morbidly obese subjects.
Methods: We studied 60 subjects (mean age 37±12 years) with morbid obesity (BMI>40 kg/m^2) by 2D, and Doppler Echocardiography 1 week before, 3 and 6 months after surgery. AoD was calculated using the formula 2 x (pulsatile change in aortic diameter)/[diastolic aortic diameter x (aortic pulse pressure)]. Aortic diameters were measured 3 cm above the aortic valve by 2D guided M-mode echocardiography and aortic pulse pressure [systolic (SBP)-diastolic blood (DBP)pressure (mmHg)] was obtained simultaneously by cuff sphygmomanometry. Samples were obtained for measurement (mg/dl) of total cholesterol (TCH), low density lipoprotein (LDL), triglycerides (TG) and glucose (GLUC).
Results: All patients had normal systolic function before and after surgery. Aortic distensibility [normal range:2.4-4.4 cm^2 dyn(-1) 10^{-6} was impaired before surgery (Table). Increased BMI was related to decreased AoD ($r=0.43, p<0.01$) before surgery. Increased LV mass was independently related to increased BMI ($r=0.47$ $p<0.01$) and reduced AoD ($r=0.40$ $p<0.01$) before surgery. Three and 6 months after surgery, BMI, LV mass (gr), TCH, LDL,TG,GLUC and SBP were all reduced, whereas AoD was increased (table, $p<0.01$). Changes in LV mass were related to changes of SBP 3 and 6 months after surgery($r=0.46$ and $r=0.47$ $p<0.01$).

Surgery	BMI	AoD	LVmass	TCH	LDL	TG	GLUC	SBP	DBP
Before (1week)	49±7	1.6±1	335±83	212±38	144±32	134±55	99±21	125±13	80±15
After (3months)	38±9	3.4±1.1	252±48	153±32	99±29	104±28	85±18	119±18	78±11
Follow up (6months)	30±7	3.8±1.1	195±48	130±30	89±20	94±21	80±15	110±10	75±11
p	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	ns

Conclusion: Morbid obesity is related with impaired aortic distensibility and increased LV mass. Weight reduction after bariatric surgery, reduces serum lipids, lowers blood pressure and thus, normalizes aortic distensibility and LV mass[2]

P598 Influence of major depression on regional cerebral blood flow in elderly patients with heart failure

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Introduction: In patients with heart failure (HF) major depression (D) has a high prevalence and a prognostic impact. Changes in cerebral perfusion have been related to D and could have a physiopathological role. However, regional cerebral blood flow (RCBF) in patients with D and HF has not been studied.
Objectives: To investigate the Regional Cerebral Blood Flow in patients with D and HF.
Methods: 20 elderly patients with HF class II and III (NYHA), and D (DSM-IV criteria and Hamilton score > 18), free of psychotropic drugs were evaluated as well as 18 non depressed elderly patients with ejection fraction of 36.5%±7.6 and 38.6% ± 8.1 respectively and matched for HF functional class (NYHA). Both groups were compared to 19 controls 71.1 ± 4.8 years old, matched for age, sex, cerebral dominance and social level. Brain perfusion was evaluated with a double-headed SPECT system (Sophy-DST), after 99mTc-HMPAO injection. Group differences were investigated using Statistical Parametric Mapping program that compares differences in RCBF voxel-to-voxel, with a $p<0.001$ with a statistical significance.
Results: Significant RCBF reductions were seen in HF relative to C in the right lateral temporal lobe, cuneus and precuneus, as well as in a small area of the medial prefrontal cortex. In HF patients with D, significant cortical RCBF reductions relative to C were seen in similar locations but more extensively. In addition, they had RCBF reductions in limbic and subcortical areas, including the right parahypocampal gyrus, posterior cingulate, thalamus and caudate at the border of the lateral ventricle, and bilaterally in the posterior insula.
Conclusions: HF leads to significant RCBF reduction, however patients with D + HF associated seem to have further reductions in RCBF, especially in limbic and subcortical areas, what could have a physiopathological role due to the relation of the limbic areas with emotional functions. Further studies are necessary to evaluate the treatment of D and HF in RCBF.

MYOCARDIAL INFARCTION – PROGNOSIS ASSESSMENT

P599 Management and outcomes of cardiogenic shock patients in a Canadian province. ICONS data

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Introduction: Cardiogenic shock following acute myocardial infarction carries a poor prognosis and a high early mortality rate. Overall mortality benefit from early revascularization of affected patients has not been convincingly demonstrated in controlled trials, especially in the short term phase. Practice patterns and outcomes of cardiogenic shock patients on a population wide level are not known.
Methods: We accessed the population-based registry of the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) that collects detailed clinical data on all patients hospitalized with acute coronary syndromes among other conditions in the province of Nova Scotia, Canada. Individuals admitted between October 1997 and June 2001 with chest pain and an increase in cardiac enzymes, as well as blood pressure below 90 systole and pulmonary congestion were identified as having cardiogenic shock and were used as subjects for this analysis. Patients had to have these features either at admission or develop shock during their hospital stay. Group 1 patients were those admitted directly to the sole tertiary care center in the province with intervention facilities and those subsequently transferred there from other sites. Group 2 patients were those managed at non-tertiary facilities. Five patients from Group 2 came for cardiac catheterization/PCI and were returned back to the non-tertiary center.
Results: On the basis of the diagnostic criteria used to define cardiogenic shock patients, a total of 354 patients were identified. Shock on admission was present in 151(42.7%) and shock developed subsequently during the hospital stay in 203 (57.3%). Respective characteristics for Group 1 (n=204) versus Group 2 (n=150) were: mean age 69.9 years Vs 74.4 years, cardiac catheterization rates 57.4% Vs 2%; PCI 21.6% Vs 1.3%; CABG 36.3% Vs 0%; In-hospital mortality 50% Vs 64%. All these differences were statistically significant. No differences were seen in history of previous MI, previous PCI, previous CABG or previous renal failure. There was no difference in the use of thrombolytic therapy between the two groups.
Conclusion: Mortality of cardiogenic shock patients even in the tertiary care center was high, although comparatively lower than patients treated at non-tertiary centers and the difference may relate to revascularization procedures. Further study into factors impeding referral of patients with cardiogenic shock to centers with interventional facilities is required.

P600 Differences in characteristics, management and outcome of patients with acute coronary syndromes hospitalized in cardiology versus medicine departments

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Background: The incidence of acute coronary syndrome without persistent ST elevation (ACS) has increased over the last decade. The mortality of patients with ACS, however, remained constant. Doctor specialty, internist vs. cardiologist, may affect the quality of care and outcome of patients with ACS. We sought to determine the effect of specialty, cardiologist vs. internist, on management and outcome of patients with ACS.

Methods and Results: From June to Sept 1999, we prospectively collected data on a cohort of 187 consecutive patients with ACS admitted to the Cardiology Department vs. 3 of 6 Internal Medicine Departments in the Soroka Medical Center. The patients were followed through the hospitalization period and over 32 months from discharge. Patients treated by cardiologists were younger (65+10 vs.61.6+11 years, p=0.03) and had high % of ischemic indexes on admission (ST elevation>1 mm: 42% vs. 7%p<0.0001; anterior ischemia: 60% vs. 26%, p<0.0001 or non Q MI 10% vs. 3%; p=0.06).

Patients treated by internists were less likely to receive aspirin (94% vs. 78%, p=0.004) or lipid lowering drugs (25% vs. 39%; p=0.02) during hospital stay. Patients treated by cardiologists were less likely to refer to early exercise test (0% vs. 5%, p<0.0001) but significantly more likely to undergo coronary angiography (63% vs. 12%, p<0.0001) and PTCA (28% vs. 5%, p<0.0001) than patients treated by internists.

By multivariate analysis, cardiologist management was associated with reduced risk for the combined primary endpoint of death, re-MI, or readmission at one year (OR=0.48; 95% CI 0.26-0.88) and 32 months (OR=0.26; 95% CI0.13-0.53).

Mortality rate at 30 days after admission was similar (0% vs.1%, p=1). However, mortality at 32 months was significantly lower in cardiology-treated patients (7% vs. 20%, p<0.0001). After multivariate adjustment, mortality after 2 years was independently associated with age (OR=1.07; 95% CI 1.02-1.12), TIPI risk index (OR=0.03; 95% CI 0.002-0.06) or in-hospital coronary angiography (OR=0.3; 95% CI 0.84-1.08).

Conclusions: We observed significant variations in patient characteristics, care and outcome of patients with ACS admitted to Cardiology vs. Medicine departments. Although most of the patients were treated in Medicine departments, high-risk patients were more likely to be treated by Cardiologists. Cardiologists used more frequently evidence-based-medicine and interventional procedures. Our findings support the use of coronary angiography in high-risk ACS patients.

P601 A prognostic risk score for 30-day mortality after acute myocardial infarction in a community-based population

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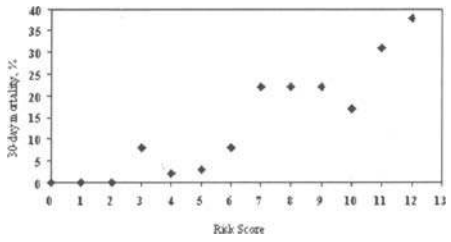
Background: Risk scoring (RS) systems to define mortality risk after acute myocardial infarction (AMI) have been developed from clinical trial data. However, trials often enroll patients who do not reflect the spectrum of risk seen in AMI, cannot track trends over time and often require information not readily available on presentation. Accordingly, we developed and validated a RS system from a large clinical database of consecutive patients evaluated over a 12-year period. Parameters included only ones available during the initial clinical evaluation.

Methods: Our cohort included 1212 consecutive Olmsted County, MN patients with AMI from January 1988 to July 2000. A RS was developed to predict 30-day mortality. The RS (0-18) was calculated as the sum of points for the following factors: age >80 (2), female gender (3), SBP ≤ 140 (3), creatinine > 1.4 (1), ST segment depression 1-2 mV (1), ST segment depression > 2 mV (3), QRS duration ≥ 100 msec (1), Killip class > I (3), and anterior location (1). The sample was split into a training set from before January 1, 1997, and a test set from after that date for development, validation and to allow evaluation of accuracy over time.



30-Day mortality by risk score.

Results: The RS predicted 30-day mortality when viewed as a continuous variable (Figure) or when divided into low (RS < 6, 3.4%), intermediate (RS 7-10, 21.4%) or high risk groups (RS > 11, 35.3%), p<0.01. Predictive ability was high in the training set (c=0.78, see Figure) and increased over time (c=0.74, 0.73, 0.82, and 0.89 for years 1997-2000, respectively).

Conclusion: Short-term survival for the entire spectrum of AMI patients can be predicted based on clinical data available on presentation. Our RS is statistically robust and should aid clinical-decision making.

P602 Geographic differences in clinical characteristics and long-term clinical outcome in the TARGET study

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Background: Gp IIb/IIIa inhibitors have consistently reduced adverse cardiac events in acute coronary syndromes and in coronary intervention (PCI). However, outcomes have varied widely by geography. TARGET compared outcomes with tirofiban (T) vs. abciximab (A) in 4809 patients (pts) undergoing PCI/stent. The primary endpoint (death, myocardial infarction (MI) or urgent revascularization at 30 days) occurred in 7.6% of T pts vs. 6.0% of A pts. Event rates were substantially different in the US compared with Non-US (7.2% US vs. 4.9% Non-US, p = <0.05) 6-month TVR was also different: US=9.0% vs. 5.4% Non -US. At 1-year FU the mortality rate was 1.9% in US group and 1.3% in non-US group.

Methods: We examined demographic, clinical, and procedural characteristics of TARGET pts by country.

Results: Mean ages were higher in US vs ex-US and a higher percentage of US pts were >75 years old. Women comprised a higher percentage of US pts. US pts weighed more, and had a higher prevalence of diabetes. A greater percentage of US pts underwent PCI for ACS. US pts had a shorter pre-procedure hospital stay. Rotational atherectomy (RA) was used more often in US. Peak ACT was lower in the US.

Geographic differences in TARGET

	US (n=3910)	Non-US (n=899)	p
Age	62.5±11.1	61.6 ± 10.1	0.023
> 75y.o.	16.3%	9.6%	0.001
Women	27.1%	23.7%	0.034
Weight (kg)	87.6	79.5	0.001
Diabetes	24.5%	17.6%	0.001
ACS	65.0%	54.0%	0.001
Admission to PCI (d)	0.57	2.24	<0.001
RA	6.5%	0.7%	<0.001

Conclusions: Despite identical inclusion criteria, significant differences in patient characteristics were identified between US and ex-US cohorts. Multivariate modeling is being performed to assess the impact of these variables on outcome.

P603 Analysis of case-fatality following coronary artery bypass grafting using an administrative database

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Background: The aim of the present study was to evaluate the case-fatality after Coronary Artery Bypass Grafting (CABG) using data from a national administrative database. All hospitalisations in Denmark where a CABG was performed at one of the five public invasive centres were studied.
Method: By linkage of the National Hospitalisation Register and the Danish Civil Registration System we were able to describe the course of 12466 CABGs from 1997 to 2000. From the Hospitalisation register we had individual data concerning date of procedure, concomitant procedures, centre, age, gender, in-hospital mortality and whether the admission was acute or elective. Information regarding mortality up to 30 days after the procedure was acquired from the Danish Civil Registration System. The outcome was total mortality in-hospital and within 30 days. Differences in case-fatality were analysed in logistic regression. The national average was used as reference.
Results: Female gender was associated with a significant increased risk of 30-day mortality independently of age, odds ratio 1.5, $p<0.0001$. An increase of age of 10 years increased the risk by 1.7, $p<0.0001$, independently of gender. After adjustment for age and gender there was no significant difference between the five centres in the case-fatality after isolated CABG when surgery was planned. The crude 30-day mortality ranged from 1.5% to 2.3%. For acute isolated CABG there was a significant difference in case-fatality between centres. The crude mortality ranged from 3.7% to 11.6%. The odds ratios estimated were 0.6, 0.7, 1.2, 1.3, and 1.9, $p<0.01$. The analyses were also performed using only in-hospital mortality as out-come. These data showed more pronounced differences between centres attributable to early transfer to other department or hospital or fast track surgery.
Conclusion: For planned CABG adjustment for age and gender explained the variation in institutional performance. For acute CABG the variation was significant after adjustment for age and gender. The odds ratios ranged from 0.6 to 1.9. We find that the administrative database has limited information to adjust for the differences in patients undergoing acute CABG. Patients undergoing planned CABG were more comparable with regard to prognosis. These patients are more comparable with regard to the pre-operative status, since there is consensus on the indication and selection of candidates for CABG. A fixed period of follow-up should be used (e.g. 30-day mortality), since in-hospital mortality is biased by transfers and early discharge.

P604 Clinical characteristics, dobutamine stress echo, and beta-blocker therapy to optimize long-term cardiac management after major vascular surgery

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Aims: Patients after major vascular surgery are at increased risk of continuing cardiac complications. We examined the relationship of clinical characteristics, dobutamine stress echocardiography (DSE) results, beta-blocker therapy (BBL), and long-term cardiac events in patients undergoing major vascular surgery.
Methods: A total of 1351 patients scheduled for major vascular surgery were screened for cardiac risk factors, including age> 70 years, prior myocardial infarction (MI), angina, diabetes mellitus, stroke, renal failure, and heart failure. DSE was performed in 1097 patients (81%) with at least one risk factor or a reduced exercise capacity. Stress induced ischemia was present in 199 patients (18%). BBLs were administrated in 360 patients (27%). A total of 1294 patients (96%) survived surgery for at least 30 days. Mean outcome measures were cardiac death or non-fatal MI during long-term follow-up, compared by clinical characteristics, DSE results and BBL use.
Results: Mean follow-up duration was 23 months (range 14-33 months); 13 patients (1%) were lost to follow-up. There were 7 (1.9%) cardiac events in 373 patients without risk factors, 33 (4.4%) events in 745 patients with 1-2 risk factors, and 33 (19%) in 176 patients with 3 or more risk factors. In patients without risk factors, BBL use reduced the risk of cardiac event (1.8% vs 0%), and DSE had no additional prognostic value. In patients with 1-2 risk factors the presence of ischemia during DSE increased cardiac events from 3.7% to 8.9%. However, if patients with ischemia were treated with BBL the risk decreased to 4.1%, comparable to patients without ischemia. In patients, with 3 or more risk factors DSE and BBL stratified patients into intermediate and high risk. In patients without ischemia BBL use reduced cardiac rate from 14% to 10%. However, in patients with 3 or more risk factors and ischemia BBL use was not protective: event rate as high as 22%.
Conclusion: BBL effectively reduces long-term cardiac events. DSE provides no additional prognostic information in patients with 0-2 risk factors, provided BBL are applied. In patients with 3 or more risk factors DSE stratifies patients into intermediate and high-risk groups.

P605 In-hospital mortality of acute myocardial infarction in relation to polymorphisms of the renin-angiotensin system genes

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Aims: The Insertion/Deletion polymorphism of the Angiotensin-Converting Enzyme (ACE) gene and the A1166C single nucleotide polymorphism of the angiotensin II AT1 receptor (ATR1) have been associated with left ventricular remodelling and prognosis after acute myocardial infarction (AMI). We investigated whether these genetic variants associate with increased risk for in-hospital mortality after AMI and whether their possible effects are mediated by their relation to the modulation of the left ventricular systolic function during hospitalization for AMI.
Methods: We studied 1629 consecutive, AMI patients (mean age 62±13 years, 79% males), enrolled in the GEMIG study (Genetic predisposition and Epidemiology of acute Myocardial Infarction in the Greek population). All patients were recruited on admission from 9 Cardiac Departments located in three cities and were genotyped for the ACE I/D and ATR1 A1166C polymorphisms utilizing polymerase chain reaction amplification techniques.
Results: The in-hospital mortality was 7.1%. Deceased patients were older (71±13 vs 62±12 years, $P<0.001$) and had lower left ventricular ejection fraction (LVEF) estimated by echocardiography (45±9 vs 33±12%, $P<0.001$). In univariate analysis the LVEF did not differ among patients with or without the DD (44.4±9.7 vs 44.4±9.6%, P=NS) or the CC genotype (44.3±9.7 vs 45.8±9.8%, P=NS). In multivariate analysis with only clinical variables included as covariates, age (RR=1.047, 95%CI=1.007-1.088, P=0.001), prior AMI (RR=2.976, 95%CI=1.158-7.647, P=0.024) and LVEF<45% (RR=6.4 95%CI=1.5-27.7,P=0.013) were significant and independent predictors of in-hospital mortality. Inclusion of the DD and/or the CC genotype in the multivariate model did not effect the results of multivariate analysis. The studied genetic variables were associated neither with in-hospital mortality nor with LVEF after AMI.
Conclusions: In this multicenter, prospective study, the I/D polymorphism of the ACE gene and the A1166C polymorphism of the ATR1 gene were not associated with short-term prognosis after AMI. In symphony with previous studies the LVEF was an independent predictor of poor short-term outcome. However, its relation with in-hospital mortality was not influenced by the studied genetic variables. Our data, derived from a large-scale specifically designed study question the role of the studied genotypes in the pathogenesis of AMI, and in contrast to previous reports in the field, do not support the hypothesis that the studied genotypes influence prognosis after AMI.

P606 Atypical presentation of acute coronary syndromes independently predicts myocardial infarction and increased in-hospital mortality: insights from the GRACE registry

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Background: Patients with acute coronary syndromes(ACS) may not experience retrosternal chest pain (atypical presentation). We interrogated a contemporary multinational registry of patients with acute coronary syndromes(GRACE) to determine clinical characteristics and prognostic significance of atypical presentations in patients with ACS.
Methods: 16,026 patients with unstable angina (UA), non-ST-segment elevation (NSTEMI) and ST-segment-elevation myocardial infarction (STEMI) from 95 hospitals in 14 countries were included in this analysis. Patients were grouped according to the presenting symptoms (atypical vs typical) and baseline characteristics and in-hospital outcomes compared.
Results: 1,324 (8.3%) of patients with ACS presented without chest pain. The most common atypical presentations were dyspnea (46.2%), diaphoresis (25.3%), nausea/vomiting (24.7%), syncope/pre-syncope (22.3%). Atypical presentation occurred in 5.5% UA, in 12.1% NSTEMI and in 8.0% of STEMI patients. When compared to patients with chest pain, those with atypical presentations were older (72.2y vs 65.7y), more likely to be female (39.7% vs 32.5%), diabetic (31.2% vs 23.5%), have a history of heart failure (22.5% vs 9.7%), to have an MI (75.2% vs 61.7%) and were less likely to be revascularised in hospital (26.5% vs 35.9%; all $p < 0.0001$). Atypical presentations were more common in the US than in Europe (14.6% vs 6.1%), and carried an adverse prognosis: in hospital death 14.2% vs 4.5%, $p < .0001$). Multivariate analysis adjusting for age, sex, diabetes, medical history and type of ACS (mortality only), revealed that an atypical presentation was independently predictive of both a diagnosis of MI and in-hospital mortality (Table).

Outcome	Adjusted OR (95% CI)
Death	2.4 (2.0-2.9)
MI	2.0 (1.7-2.3)

In-Hospital Outcomes for Atypical Presentation (vs Typical)

Conclusions: Atypical presentation of ACS is independently associated with an adverse outcome. These high risk patients merit close in-hospital monitoring and where appropriate, early aggressive management directed toward improving their outcomes.

P607 Low-risk patients with chest pain and without evidence of myocardial infarction may be safely discharged from emergency department

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Introduction: In previous studies, 2 - 8% of patients with myocardial infarction (MI) have been inappropriately discharged from emergency departments due to missed diagnoses of MI. Usually, these patients have had adverse prognosis. The purpose of this study was to investigate the prognosis of patients with chest pain attack, in whom MI was ruled out and in whom there was no evidence of high-risk acute coronary syndrome on the basis of history, clinical examination, electrocardiogram (ECG) and biochemical markers of myocardial injury, and who were discharged from emergency room (ER) or adjacent chest pain observation unit (CPU).
Methods: This study is a part of a clinical audit of the management of 3718 consecutive patients admitted to the emergency department of the Kuopio University Hospital due to chest pain or cardiac arrest during the period from 1 January 1997 until 31 December 1999. MI was ruled out in 2636 (71%) patients, and 1317 (50%) of them were discharged to home from the ER or CPU within 24 hours from admission. The patients were retrospectively identified from the outpatient clinic register and hospital discharge register. One-week, 4-week, 3-month, and 6-month mortality data were received from the national Causes-of-Death Register.
Results: After observation, of the 1317 patients (672 men and 645 women; mean age 58 years) 855 (65%) were discharged from the ER and 462 (35%) from the CPU. The patients discharged from the ER were younger than those discharged from the CPU (mean age 54 vs 64 years; $p < 0.001$). One-week mortality after the discharge from the ER was 0% and from the CPU 0%. Four-week mortality was 0.2% and 0.6%, 3-month mortality 1.3% and 1.9%, and 6-month mortality 1.8% and 3.2%, respectively.
Conclusions: Patients admitted to the ER or the CPU with chest pain may be safely discharged within 24 hours from admission, if there is no evidence of MI or high-risk acute coronary syndrome on the basis of history, clinical examination, ECG, and biochemical markers.

P608 Is coronary angiography performed in the appropriate patients after myocardial infarction? A study in 2493 patients (the PRIMA study)

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Objective: Rates of coronary angiography after myocardial infarction vary widely between institutions. Furthermore, the indications for coronary angiography are often in conflict with recognized guidelines. The present study sought to determine the characteristics and the one-year mortality in patients with myocardial infarction, regardless of age and hospital facilities, according to the use of coronary angiography after myocardial infarction.
Methods: Data were prospectively collected in all patients with myocardial infarction admitted to all hospitals in three departments in the Rhône-Alpes region.
Results: Among 2,493 patients, 1,117 (45%) underwent coronary angiography within 3 months after myocardial infarction (median delay: 10 days). Coronary angiography was performed in 89% of the patients * 45 years old, 65% of the patients 45-70 years old and 18% of the patients * 70 years old ($p < 0.0001$). In multivariate analysis, coronary angiography rate was lower with older age (odds ratio [OR]: 0.40 for 10 years), female gender (OR: 0.54), in patients with comorbidity (OR: 0.62) or heart failure (at admission: OR: 0.68; worsening of heart failure during the first 5 days: OR: 0.71). It was higher in patients with non-Q wave myocardial infarction (OR: 1.93) and in patients who had thrombolysis (OR: 1.49). Coronary angiography was performed in 49% of patients admitted to hospitals with on-site coronary angiography vs 32% in hospitals without on-site coronary angiography (OR: 3.54, after adjustment for patients' characteristics). One-year mortality rate was 6.5% for the coronary angiography group and 36.9% for the no-coronary angiography group. In multivariate analysis, age, history of angina pectoris, presence of Q waves, Killip class at admission II, III, or IV and CPK ratio * 9 were significant predictors of a higher one-year mortality, but performance of coronary angiography did not significantly influence it: RR: 0.79 (95% CI 0.58 to 1.07).
Conclusions: Among patients with myocardial infarction in a large unselected cohort in a French region, the one-year mortality was significantly lower in those referred for angiography. However, after correction for the confounding effects of simple baseline clinical indicators of risk, this apparent benefit reflected the fact that angiography was performed in those at lowest risk.

P609 Influence of known arterial hypertension on hospital mortality of acute ST-segment elevation myocardial infarction: results of MITRA and MIR

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Background: Arterial hypertension (HT) is a main risk factor for the development of cardiovascular disease. The influence of previously known HT on prognosis of acute ST-elevation myocardial infarction (STEMI) has been discussed very controversially.
Methods: The German Registries MITRA and MIR included 21441 consecutive patients with STEMI between 1994 and 2000. The hospital and long-term mortality (18 months, MITRA) of STEMI-patients with and without previously known HT were compared.
Results: Out of 21441 consecutive STEMI-patients 8485 had a previously known HT (40%). STEMI-patients with known HT were older (69 vs 67 years, $p<0.001$), more often had prior STEMI (19.3 vs 14.7%, $p<0.001$), diabetes mellitus (35.0 vs 16.4%, $p<0.001$) and a 35 min longer prehospital delay ($p<0.001$). Patients with known HT received acute reperfusion for STEMI significantly less often (45.6 vs 52.3%, $p<0.001$). Despite this worse risk profile, patients with known HT had a significantly lower hospital mortality as compared to STEMI patients without history of HT (13.2 vs 16.3%, $p<0.001$). Within a follow-up of 18 months after acute STEMI, patients with history of HT more often had myocardial reinfarctions (3.0 vs 2.3%, $p<0.01$). Long-term-mortality in patients with known HT was 28% higher than in patients without previously known HT. After correction for age, differences in baseline characteristics and acute therapy using a logistic regression model, hospital mortality was lower in patients with known HT whereas long-term mortality was not different in both groups (table).

Influence of HT on outcome of STEMI

Parameter	Odds Ratio	CI 95%
Hospital Mortality	0,86	0,78-0,96
18-months Mortality	0,99	0,79-1,25

Conclusion: STEMI-patients with previously known HT had a 14% lower hospital mortality as compared to patients without known HT. Long-term mortality within 18 months after the index STEMI was similar in patients with and without known HT.

P610 Early missed diagnosis of acute myocardial infarction: patients at risk and in-hospital mortality

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Background: Acute myocardial infarction (AMI) may present with atypical or no chest pain and/or with unspecific ECG changes and may therefore be missed initially. To assess which patients are at risk for such "early missed diagnosis" and what their inhospital outcome is, we performed a retrospective chart analysis.
Methods: Charts of 247 consecutive patients (pts) with the discharge diagnosis of AMI between 7/2000 and 6/2001 were retrospectively analysed. The initial ECG was reanalysed and compared to initial and final diagnoses. All relevant data regarding coronary artery disease and hospitalisation were collected and compared between pts with and without the initial diagnosis of AMI.
Results: Of the 247 pts, 120 (49%) were 75 years or older (elderly: 81 ± 7 years versus 65 ± 10 years in pts under 75 years), 98 (40%) were women. The initial diagnosis was other than acute coronary syndrome in 25% of elderly versus 7% of younger pts ($p<0.0001$) and 22% in women versus 11% in men ($p<0.05$). The missed AMI diagnosis in the initial ECG was higher in elderly pts (29% versus 8%, $p<0.001$) whereas there was no significant influence of gender. Comorbidity was higher in the elderly pts (74% versus 30%, $p<0.0001$) and also non-cardiac disease with a presumed life-span < 1 year (19% versus 5%, $p<0.001$). At entry 31% of the elderly and 16% of the younger were without anginal pain ($p<0.01$), but the strongest predictor for presenting without chest pain was female gender (36% versus 15%, $p<0.001$). Most of the pts without pain had only dyspnea (46%) or general weakness (18%). An other predictor of no pain at presentation was mental disorder in elderly pts (14% versus 0%, $p<0.005$). Inhospital mortality was higher in pts with early missed versus correct diagnosis (33% versus 13%, $p<0.005$), but no difference was found in outcome between age groups.
Conclusion: AMI may present without chest pain particularly in elderly pts, women and pts with mental disorders. In addition, early ECG changes are unspecific in almost 1/3 of elderly pts. Still, pts with such a missed early diagnosis of AMI have a three times higher in-hospital mortality than pts with correct diagnosis. Therefore, early diagnosis of AMI has to be actively sought for, particularly in elderly women presenting with dyspnea.

P611 Angiotensin-converting enzyme inhibitor use predicts increased risk of death and recurrent myocardial infarction among patients receiving aspirin after myocardial infarction

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Background: Both aspirin (ASA) and Angiotensin converting enzyme inhibitors (ACE-I) have established benefit in reducing ischemic events after myocardial infarction (MI). Some evidence suggests that ASA may attenuate the beneficial effects of ACE-I among patients with CAD or left-ventricular dysfunction. There is controversy regarding their concurrent use and the appropriate dose of ASA among patients receiving ACE-I.
Methods: We examined the relationship between the combined use of ACE-I and ASA and clinical outcomes among patients after MI randomized to three different anticoagulant/ASA regimens in the Coumadin Aspirin Reinfarction Study. On presentation, patients were randomized to one of three treatments: 160mg ASA, 80mg ASA + 1mg warfarin, 80mg ASA + 3mg warfarin. The groups receiving the 80mg ASA dose were combined for this analysis.
Baseline characteristics and the percentage of patients taking ACE-I at study entry were defined. A Cox proportional hazards model was utilized to assess the association between ACE-I use, ASA dose and the end-point of death or recurrent MI.
Results: Data from 8796 patients were analyzed (99% of study population). Median duration of follow-up was 14 months. 2310 (26.2%) patients were receiving ACE-I at enrollment. Patients receiving ACE-I tended to be older (61 vs. 58, $p<0.001$), have diabetes mellitus (28% vs. 16%, $p<0.001$), and have heart failure (23% vs. 6%, $p<0.001$). Ejection fraction was lower among patients receiving ACE-I (45% vs. 55%, $p<0.001$).
After adjusting for important co-variates, patients receiving an ACE-I with ASA had a higher rate of death or recurrent MI compared to those receiving ASA alone (HR=1.22, 95% CI=1.04-1.43, p=0.013). There was no significant interaction between ASA dose and the effect of ACE-I use on the above endpoint (p=0.69).
Conclusions: Patients receiving ASA and ACE-I after MI have higher rates of death and recurrent MI compared to those receiving ASA alone, this difference persists after adjusting for important prognostic factors. The higher rate of adverse outcomes with this combination is present even in those receiving "low-dose" (80mg) ASA. Prospective studies are needed to clarify the interaction(s) between these agents.

P612 Cardiovascular mortality and morbidity in chronic haemodialysis patients: CORDIAL, a 3-year follow-up cohort study

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Introduction: Chronic hemodialysis (HD) patients are at high risk of cardiovascular (CV) events and death. No therapeutic intervention aimed to prevent CV outcome has been tested in prospective randomised clinical trials in such patients. Assessing the rate and the determinants of CV events in HD patients is critical for the design of future clinical trials and therapeutic strategies in patients with this condition. This was the aim of CORDIAL (Cardiac Outcome Registry in DIALysis), a prospective observational cohort study with a 3 year follow up period.

Methods and results: Among a total of 685 patients registered in 11 HD centres in the east of France during year 1996, a cohort of 378 patients aged 50 years to 80 years, on dialysis for more than 3 months was identified. They were aged 66±7 years, 59% were male, 46% had a history of CV disease (17% heart failure, 10% MI, 20% angina, 6% stroke), 18% had diabetes. At baseline blood pressure was 139/74 +24/14 mmHg, hemoglobin 10.5±1.8 g/dL, Kt/V 1.48±0.35. Echocardiography was available in 304 patients and showed a LV mass index at 155±51 g/m^2 and LVEF at 64±13% (30% pts had LVEF<45%). Total mortality was 15% at 1 year and 41% at 3 years (9% and 24% respectively were related to a CV cause). One year mortality was 8 fold (and CV death 13 fold) superior to that observed in age and gender matched general population in eastern France. Combined death and CV non fatal event rate was 39% at one year and 70% at 3 years. In multivariate analysis, the following factors were shown to be independently associated to total mortality: diabetes (RR=2.0[95%CI=1.3-2.9]), CV disease history (2.1[1.5-3.1]), age>70 (1.6[1.1-2.3]), LV mass index>median (1.9[1.2-2.8]) and duration of dialysis>10yrs (2.1[1.4-3.2]). Only CV disease history was independently associated to CV mortality (2.3[1.4-3.8]). Male gender (2.0[1.2-3.3]), history of CV disease (2.1[1.3-3.3]), and age>70 (1.8[1.1-2.8]) were associated to CV fatal and non fatal events.

Conclusion: Chronic hemodialysis patients aged 50 to 80 are at excessive risk of CV death and CV events. LV hypertrophy is very prevalent and is a predictor of total mortality. The CORDIAL cohort provides epidemiological observational community based prospective data which may be useful for sample size calculation and design of much needed CV prevention clinical trials in hemodialysis patients.

P613 Do differences in characteristics or in management account for the poorer outcome after myocardial infarction in diabetics? The PRIMA study

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Background: There is an excess mortality after myocardial infarction in diabetics, but also documented significant differences in the characteristics of myocardial infarction and in management between diabetics and non-diabetics. The aim of this prospective study in a large unselected patient cohort in a single French region was to determine if baseline characteristics, management, or in-hospital and one-year mortality differed in diabetic and non-diabetic patients with myocardial infarction.

Methods: Data were prospectively collected in consecutive patients with myocardial infarction admitted to all hospitals in 3 departments in the Rhône-Alpes region between 09/01/1993 and 01/31/1995.

Results: Among the 2,297 patients, 410 patients (17.8%) were diabetic. The proportion of diabetics was almost 4 times greater in the PRIMA population than the expected rate in a cohort of the overall French population with a comparable age distribution. Although diabetics were older than non-diabetics (70.3 vs 67.8 years; p < 0.0004), and less likely to receive thrombolysis (31% vs 36%; p = 0.043), in-hospital mortality was not significantly higher (17.3% vs 14.7%) than in non-diabetics. Coronary angiography was performed significantly less frequently in diabetics than in non-diabetics (39% vs 46%; p = 0.015). Left anterior descending artery disease was more frequent in diabetics than in non-diabetics (67% vs 58%). Reinfarction and use of CABG or of PTCA did not differ significantly between diabetics and non-diabetics. One-year mortality rate was significantly higher in diabetics (31% vs 22%; p = 0.001) than in non-diabetics. In multivariate analysis, diabetes was a significant predictor of one-year mortality (relative risk: 1.41; 95% CI = 1.10 - 1.79; p = 0.0063) but not of in-hospital mortality (relative risk: 1.2; 95% CI = 0.9 - 1.7; p = 0.25). Multivariate predictors of in-hospital and one-year mortality in diabetics were age and Killip class at admission.

Conclusions: In this large unselected French cohort, diabetes mellitus was a significant predictor of one-year but not of in-hospital mortality after myocardial infarction in a French region. This pejorative effect of diabetes on mortality was not related to differences in baseline characteristics, or in initial or post-discharge management between diabetics and non-diabetics.

P614 Coronary angioplasty in acute coronary syndromes – impact of stents and Gp-IIb/IIIa blockers beyond randomized trials

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Randomized clinical trials have shown that the use of stents or Gp-IIb/IIIa receptor blockers in patients with an acute coronary syndrome receiving coronary interventions improves clinical and angiographic outcome. Whether these results can be transferred to a real world collective has not been settled. We analyzed the influence of stents and Gp-IIb/IIIa blockers on the clinical and angiographic outcome in a consecutive series of 1103 emergency angioplasties in patients presenting with an acute coronary syndrome.

Patients suffered from unstable angina (UA) in 51% and acute myocardial infarction (MI) in 49%. Rates of stenting increased from 10% before 1997 to 65% in 2001. Angiographical success rates (TIMI 3 flow and <50% residual stenosis) and minimal lumen diameter post angioplasty were significantly higher after stenting (98.5%, MLD 2.63±0.54 mm) compared with balloon dilation alone (84.1%, MLD 1.81±0.78 mm; p<0.001). In-hospital mortality was significantly higher in patients suffering from MI (9.8%) compared with UA (3.0%, p<0.01), but did not differ in patients with (6.6%) and without (6.1%) stenting. Patients with TIMI-3 flow after angioplasty had received more often Gp-IIb/IIIa blockers compared with patients having TIMI 0-2 flow (ns). In-hospital mortality was strongly correlated to the success of the intervention and was 4.9% in patients with TIMI-3 and 16.9% in patients with TIMI 0-2.

Out of 1034 patients discharged from the hospital, 92% received clinical and 48% angiographic follow-up after median 228 days. Free of angina were 68% of the MI and 58% of the UA patients (p<0.02), with no difference in patients with and without stents. Occurrence of myocardial infarctions during follow-up was more frequent in MI patients (4.7%) as compared with UA patients (1.4%, p<0.01). Patients with stent implantation had significantly less major adverse cardiac events (death, MI, re-PTCA, CABG) than patients with PTCA alone (30% vs 37%, p<0.04). Angiographic subgroup analysis revealed, that restenosis rate was significantly lower (33% vs 46%, p<0.01) and MLD at follow-up was significantly higher in stented compared with non-stented lesions (1.70±0.91 mm vs 1.30±0.89 mm, p<0.001). Occurrence of restenosis did not differ between patients with MI and patients with UA.

The beneficial results of stents and Gp-IIa/IIIa blockers are preserved in daily practice. Stenting in acute coronary syndromes does not reduce the in-hospital mortality, but improves the clinical long-term result and lowers the angiographic restenosis rate.

P615 Relative role of troponin I and acute-phase reactants to predict outcome in patients with non-ST-segment elevation acute coronary syndrome

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Background: Myocardial damage markers and acute-phase reactants have been related to long-term outcome of non-ST-segment elevation acute coronary syndromes (NST). We analysed the adjusted predictive power of these variables to establish the in-hospital prognosis of patients admitted for NST.

Method: The study group was composed by 518 consecutive patients admitted in our institution with a diagnosis of NST. A conservative strategy was applied. Clinical and electrocardiographic (ECG) data, Troponin I (TnI), high-sensitivity C-reactive protein (CRP) and Fibrinogen (Fb) were prospectively recorded. Only major events (death and myocardial infarction) were considered. The cut-off values of biochemical data were determined by means of their ROC curves to predict major events.

Results: During admission 19 exitus (3,7%), 16 infarctions (3,1%) and 35 major events (6,8%) were registered. In the univariate analysis major events were more frequent in patients with CRP> 14 mg/l (13,7% vs 2% p<0,01), Fb> 5 g/l (10,9% vs 2,8% p<0,01) and TnI> 3 ng/ml (11,3% vs 3,2% p<0,01); in the multivariate analysis (including clinical risk factors, heart failure at presentation, ECG changes and biochemical data) only age (OR 1,07 [1,02-1,12] per year; p<0,01) and CRP> 14 mg/l (OR 5,2 [1,8-14,8] p<0,01) were independent predictors; by quartiles of CRP: 1%; 4%; 5%; 16,3% (p<0,01). The only independent predictor of myocardial infarction was Fb (OR 1,4 [1,07-1,9] per 1 g/l increase; p=0,02). In the multivariate analysis, in-hospital cardiac death was related to age (OR 1,1 [1,03-1,2] per year; p<0,01), insulin-dependent diabetes (OR 3,9 [1-16,1] p=0,05) and CRP> 14 mg/l (OR 15,6 [1,9-127,4] p=0,01). Troponin I was associated with major events (p<0,01) and death (p=0,01) in the univariate analysis but it was not an independent predictor in any case.

Conclusions: The acute-phase reactants C-reactive protein and Fibrinogen add independent information to clinical variables in the short-term risk stratification of patients admitted for a NST-ACS. The in-hospital predictive power of Troponin I decreases when corrected by these variables.

P616 Prognostic value of D-dimer assay in patients with non-ST-segment elevation acute coronary syndromes

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In patients (pts) presenting symptoms consistent with an acute coronary syndrome, risk stratification plays a pivotal role in management decisions and improving outcomes. An earlier marker of plaque rupture could provide an important advantage over markers such as the cardiac-specific troponins (cTn), which later identify myocardial cell injury, the downstream effect of a plaque rupture event. D-dimer (DD) is the end product of the ongoing process of thrombus formation and fragmentation at the site of active plaques.

Aim: To evaluate the prognostic value of DD levels on admission in pts with non-ST-elevation acute coronary syndromes.

Methods: We prospectively studied 105 pts without co-morbid conditions known to increase DD levels. DD was measured on admission using a quantitative fibrin-specific ELISA. CTn I was measured on admission and every 6 hrs during 24 hrs. Primary endpoint was time to death or nonfatal myocardial infarction (MI) during the first 30 days after admission. Additionally, overall mortality was assessed at 1-year follow-up. For endpoint analyses, we dichotomized DD levels into their top (>470ng/ml) and lower 2 risk tertiles and used the max cTn I level (normal<0.1ng/ml).

Results: CTn I was elevated in 55 pts. At 30 days follow-up, death or nonfatal MI had occurred in 20.0% pts with DD>470ng/ml (vs 5.7% in remaining pts, log rank p=0.02) and in 16.4% pts with elevated cTn I (vs 4.0% in remaining pts, log rank p=0.04). Pts with both markers positive (n=22) were at highest risk (31.8% endpoint rate, p=0.001 vs remaining pts). After adjusting for baseline clinical characteristics, ECG findings and max cTn I level (Cox regression analysis), DD>470ng/ml was an independent predictor of 30-day outcome (hazard ratio 3.7; 95%CI 1.1-12.6; p=0.038). At 1-year follow-up, pts with DD>470ng/ml showed increased mortality (17.1% vs 4.3% in remaining pts, log rank p=0.023).

Conclusion: The DD level is a powerful independent predictor of outcome in pts with non-ST-elevation acute coronary syndromes. Future prospective trials are needed to evaluate if higher DD levels identify a subset of pts who may benefit from more aggressive antithrombotic strategies during hospitalization and more aggressive management during long-term follow-up.

P617 Application of a validated simple risk model to a non-STEMI population

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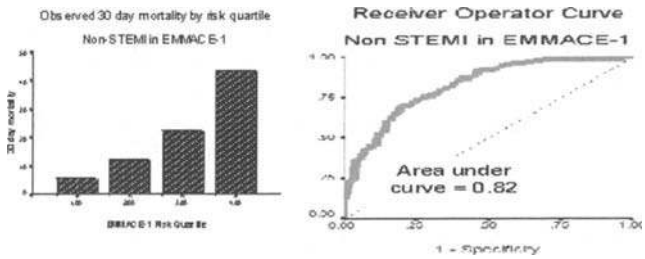
Background: Recently, in an unselected AMI population, we have developed a simple risk model to predict 30-day mortality, based on three admission characteristics: systolic blood pressure, age and heart rate. We examined the utility of this model in a non-STEMI cohort of patients.

Methods: From coronary care registers, biochemistry record and hospital management systems, 2,153 consecutive patients with confirmed acute myocardial infarction were identified, of which, 899 had a non-STEMI event. Stratification was performed on the basis of admission ECG and included patients presenting with a normal ECG, with ST depression or with isolated T wave changes. Patients with ST elevation, bundle branch block or a cardiac arrhythmia were excluded. The three variable risk model to predict 30-day mortality (P30 = 1/(1+exp(-L30) and L30= -5.624 +(0.085 x age) + (0.014 x heart rate) – (0.022 x systolic blood pressure)) was assessed within our non-STEMI population.

Results: Using multivariable logistic regression the area under a receiver operating characteristic curve was 0.82 (CI 0.78-0.86), as compared to 0.77 (0.75-0.80) for the ROC value obtained from the whole AMI population.



Conclusion: This model, derived and validated from an unselected AMI population, and based on characteristics easily available at the time of initial triage, represents a simple clinical tool to allow appropriate risk stratification of non-STEMI patients. Its performance appears at least as robust at predicting 30-day mortality as other more complicated published risk tools.

P618 Predictors of 6-month mortality in high-risk patients undergoing percutaneous coronary intervention

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Introduction: Percutaneous coronary interventions are widely applied in high-risk patients and are associated with increasing success. In this study, we looked at the determinants of the 6-month mortality in 4447 high-risk patients who underwent PCI in the GUARDIAN trial.

Materials and Methods: The clinical and angiographic characteristics and procedure related events prospectively collected in the database were reviewed. The indication for PCI was non-ST segment elevation acute coronary syndrome in 1656 patients (37.3%) and an elective procedure for a complex lesion (2 type B or 1 type C characteristic) in 2791 patients (62.7%). Odds ratios (OR) and p values were calculated for a number of variables and independent predictors of mortality at 6 months assessed by multiple logistic regression models.

Results: Death at 6 months occurred in 159 patients (3.6%). A stent was implanted in 72% of patients By multivariate logistic regression analysis, the independent predictors of mortality at 6 months were: history of CHF (OR 2.96), procedure-related complications (OR 2.52), prior CABG (OR 1.90), urgent intervention (OR 1.85), use of lipid lowering agents (OR 0.54), age<65 (OR 1.84), type C lesion (OR 1.63), history of vascular disease (OR 1.56), use of thienopyridines (0R 0.66), PCI for unstable angina (OR 1.48) and diabetes (OR 1.36); all p values were < 0.05.

Conclusions: Despite progress in stent technology and pharmacology, 6-month mortality following high-risk PCI remains elevated. Most predictors of mortality identified in the study are amenable to corrective measures.

P619 Comparison of current risk classifications in non-ST-segment elevation acute coronary syndromes. Preliminary results of RESCUER registry

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Background: Early risk stratification in patients with non-ST segment elevation acute coronary syndromes (NSTE ACS) indicates the strategy of management. Current guidelines identify high risk patients who warrant early aggressive therapy. However, there are limited data on prospective evaluation of this group of patients and on a direct comparison of various risk classifications, such as ACC/AHA, ESC, TIMI Risk Score (TRS) and simplified TIMI Risk Score (sTRS). We investigated a direct, prospective comparison of the above risk classifications for identifying high-risk group in an unselected population of NSTE ACS.

Methods: RESCUER is a prospective, multicenter, web-based registry of patients with NSTE ACS from 10 centres in Poland. Consecutive patients with symptoms of unstable angina within 24 hours were classified according to ACC/AHA, ESC and TIMI risk classification. Cardiac troponin I and CK-MB were routinely measured by on-site quantitative analysis of the Dade Behring's assays. Patients were monitored during hospitalisation and followed for 6 months. All data were collected by electronic CRFs into a web-based database.

Results: Patients admitted to participating hospitals were stratified on admission according to each classification. Data of the first 225 patients (mean age: 65±12, 55% males) were available for the analysis. High risk group characteristics and in-hospital follow-up are shown in the table.

High Risk Profile	ACC/AHA	ESC	TRS > 4	sTRS=3
n (% total group)	150 (66)	145 (64)	39 (17)	42 (18)
% in-hospital MACE*	9	11	8	17
% MI diagnosed < 24 h	56	62	70	83

*MACE: death, MI > 24h, urgent revascularisation

Significantly higher number of patients was classified into high risk group by ACC/AHA and ESC as compared to TIMI classifications (p<0.0001). 47% of NSTE ACS patients were classified consistently by ACC/AHA and ESC classifications as a high risk group, but only 9% by all tested classifications.

Conclusions: There are substantial differences between currently used risk classifications.

P620 White blood cell count and long-term mortality after non-ST-segment elevation acute coronary syndrome treated with a very early revascularization

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Background This study sought to evaluate the predictive value of white blood cell count (WBC) on short and long-term mortality in patients with non-ST-elevation acute coronary syndromes (NSTACS) treated with an very early invasive strategy.
Methods We conducted a prospective cohort study in 1391 consecutive patients with NSTACS undergoing coronary angiography and subsequent coronary stenting of the culprit lesion as the primary revascularization strategy within 24 hours. Patients were stratified according to quartiles of WBC determined on admission. The patients were followed for a mean of 20 months.
Results Kaplan-Meier survival analysis demonstrated a cumulative 3-year survival of 93.8% in the first quartile of WBC (<6.8 nL-1), 94.4% in the second quartile (6.8-8.0 nL-1), 95.1% in the third quartile (8.0-10.0 nL-1), and 82.4% in the fourth quartile (>10.0 nL-1) at 36 months ($p<0.001$ by log-rank). Relative to patients in the three lower WBC quartiles, patients in the highest quartile were three times more likely to die during the hospitalization (hazard ratio 3.2, 95% confidence interval 1.5 to 7.1; p=0.003) and during long-term follow-up (hazard ratio 3.4, 95% confidence interval 2.2 to 5.3; $p<0.001$). By multivariate Cox regression analysis including baseline demographic, clinical and angiographic covariables, WBC in the highest quartile remained a strong independent predictor of mortality (hazard ratio 3.3, 95% confidence interval 1.9 to 5.6; $p<0.001$).
Conclusion WBC count is a strong independent predictor of short and long-term mortality after NSTACS treated with very early revascularization.

P621 Aggressive time management strategies in acute myocardial infarction reduce duration of hospitalisation and mortality. Results of 346 consecutive patients

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Treatment of acute myocardial infarction (AMI) has undergone dramatic changes due to new interventional techniques and improved thrombolytic agents. Recent studies have pointed to favourable results with either a combination of GPIIb/IIIa-Inhibitors and reduced dose of thrombolytic agents or primary PCI under protection of GPIIb/IIIa-Inhibitors.
By January 1st 1999 we started a new AMI treatment program using either GPIIb/IIIa-Inhibitors and reduced dose of thrombolytic agents, if possible prehospital, or primary PCI. Decision in each case was based on the intention to minimise any time delay to reopening of the infarct related artery. For an optimal decision-process we installed a hot-line between emergency team and cardiologist.
By January 2002 132/346 patients were treated with GPIIb/IIIa-Inhibitors and half dose of a thrombolytic agent (55/132 prehospital), 214/346 underwent primary PCI. Overall median age was 61 years, 23% of the patients were women and anterior and posterior MI were equally distributed. Median time between onset of symptoms and beginning of thrombolytic therapy or PCI amounted to 4:00 hours. Maximum level of creatinekinase reached a median of 27.9 µkat/l, median left ventricular ejection fraction was 52%. The median length of hospital stay was 6.1 days. 146/346 patients (42%) did not require ICU treatment. Despite time between onset of symptoms and therapy was 4:00 hours, overall inhospital mortality was 3.7% (13 patients), mortality excluding cardiogenic shock was 0.3%. In Addition non-fatal major adverse cardiac events occurred in 4.0%.
We conclude that our new, time optimising concept is safe and effective. Inhospital mortality and overall inhospital stay can be reduced significantly.

P622 Association between the PIA platelet glycoprotein GP IIIa polymorphism and survived myocardial infarction and extent of CAD in 397 males

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Background: Several reports since 1996 have suggested the PlA2 allele of the PlA GPIIIa polymorphism of the gene encoding for GPIIIa subunit of the platelet membrane receptor glycoprotein (GP) IIb/IIIa as a significant risk factor for thrombotic complications of coronary artery disease (CAD). The objective of the current investigation was to examine the potential association between the PlA GPIIIa polymorphic variants and survived myocardial infarction and the extent of angiographically confirmed CAD.
Methods: The study was performed in 397 male Caucasian patients from the north region of Poland with significant coronary artery stenosis confirmed by elective coronary angiography. Screening for the PlA GPIIIa genotypes was performed by polymerase chain reaction of genomic DNA, followed by NciI digestion and agarose gel electrophoresis.
Results: The genotype distribution of the PlA GPIIIa polymorphism in our study group was; PlA1/A1- 75%, PlA1/A2-24% and PlA2/A2-1% with PlA1 and PlA2 allele frequencies 0.87 and 0.13, respectively. We found no evidence of association between the PlA2 allele and survived myocardial infarction OR 1.12 (95%CI 0.70-1.79), p=0.63 in the whole study group. In addition there was no association between the PlA GPIIIa polymorphic variants and survived myocardial infarction either in patients below 60 years of age (n= 236) OR 0.95 (95%CI 0.52-1.75, p=0.86) or low risk subgroup (BMI<26 kg/m^2 and total cholesterol <250 mg%) (n= 103) OR 1.30 (95%CI 0.52-3.29, p=0.57). The prevalence of the homozygous PlA1/A1 genotype among subjects with multiple-vessel CAD (two or three >50% stenosed vessels) was significantly higher than in patients with single-vessel disease; the odds ratio of PlA2/A2 or PlA1/A2 patients for having multiple-vessel CAD was 0.46 (95%CI 0.27-0.77), $p<0.003$. Also, the mean CAD score for PlA1/A1 patients was significantly lower in comparison to PlA2/A2 and PlA1/A2 patients; 7.58+2.20 and 6.98+2.37 ($p<0.03$), respectively.
Conclusions: Our results from this relatively large sample of Caucasian male patients with significant coronary artery stenosis suggest that the PlA GPIIIa gene polymorphism is not associated with survived myocardial infarction but the PlA1/A1 genotype may be associated with more severe CAD.

P623 Less acute treatment and exsessive hospital mortality of STEMI in female diabetics: results of the MITRA- and MIR-registries

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Background: Patients (pts) with known diabetes and acute STEMI are on increased risk of hospital mortality. Recent studies have shown an increased risk of female as compared to male STEMI pts. It is unknown if the female gender does have an additional impact on the hospital course in the subgroup of diabetic STEMI pts.
Methods: We analysed the prospective data of 6502/28401 (23%) unselected STEMI-pts with known diabetes mellitus of two German STEMI-registies MITRA (Maximal Individual Therapy of AMI Registry) and MIR (Myocardial Infarction Registry) to identify the impact of female gender on acute treatment and on hospital outcome.
Results: Out of the 6502 diabetic pts with STEMI 3043 (23%) were female. Female diabetics were older and had more often prior myocardial infarction and concommittant diseases as compared to male diabetics.
After adjusting for these differences in baseline characteristics, female gender was an independent determinant against acute reperfusion therapy (OR 0. 72, 0.65-0.81) and against β-blocker therapy (OR 0.83, 0.74-0.93) of STEMI in diabetics. Associated with the lower frequency of acute therapy of STEMI, female diabetics had a significantly increased hospital mortality as compared to male diabetics (OR 1.27, 1.09-1.49).

Gender differences in diabetics

	Female diabetics	Male diabetics
Age (years)	75	68
Prior STEMI	25,7%	20,2%
Hypertension	63,5%	57,4%
Acute Reperfusion	34,2%	47,5%
β-blockers	47,9%	57,8%
ACE-inhibitors	62,8%	63,7%
Aspirin	89,2%	92,1%

$p<0,05$ for all parameters

Conclusion: Female diabetic STEMI pts were less likely to receive acute reperfusion therapy than diabetic men. Within the diabetic STEMI pts with already significantly increased risk of hospital mortality compared to non diabetics, female diabetics had an additional 27% increased risk of hospital mortality after STEMI as compared to male diabetics.

P624 Type of disease onset and hospital survival in patients with myocardial infarction

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Goal. To study an association between type of myocardial infarction (MI) onset and risk of in-hospital death within the first three weeks of disease.
Methods: A retrospective analysis of 420 randomly selected hospital medical records of patients with acute and subsequent MI was done. Two binary variables related to MI onset were considered: the presence of typical pain (TP) syndrome (in keeping with WHO-MONICA criteria), and the presence of unstable angina (UA) syndrome preceding MI development. The following factors were selected as potential confounders: sex; age; acute or subsequent MI; Q-wave or non-Q-wave MI; anterior, inferior or other MI location. The association between presence of TP and UA and potential confounders was assessed by chi-square test for contingency tables with calculation of odds ratios (OR). The relative risk (RR) of death within 21 days of hospitalization was studied in Cox regression models with above mentioned variables as independent covariates. All analysis was done in SPSS 9.0 for Windows.
Results: Overall, TP was present in 60.0% and absent in 32.9% of cases; pre-MI UA was recorded in 33.3% and was not in 59.5%; in 7.1% of records a retrospective judgement on both variables could not be made. There was an inverse relation between presence of TP and UA (OR 0.50; 95% CI 0.27-0.92). Univariate analysis showed no association of TP or UA with sex, age and MI location; meanwhile TP was more frequent in Q-wave than in non-Q-wave MI (OR 2.9; 95% CI 1.5-5.4), and UA - in subsequent than in acute MI (OR 1.8; 95% CI 1.1-3.0). Cox regression model with only TP and UA as covariates showed an increased risk of death with TP presence (RR 2.2; 95% CI 1.5-3.2) and decreased - with UA history (RR 0.65; 95% CI 0.45-0.93). No evidence of interaction between TP and UA, as well as of their time-dependency, was found. Introduction of potential confounders into regression models provided no significant impact on the above associations: RR for history of UA remained unchanged (0.65; 95% CI 0.42-0.97), while RR for TP syndrome was somewhat reduced (1.8; 95% CI 1.2-2.7).
Conclusion: The presence of TP at MI onset is associated with 80% higher risk of hospital death within first three weeks; the association is independent of patients' sex and age, of MI location, of whether MI is acute or subsequent, and, probably, is partially mediated by MI type (Q-wave or non-Q-wave). The history of pre-MI UA confers 35% lower risk of hospital death independently of patients' sex and age, MI type, location, and acute or subsequent nature.

P625 Beneficial effects of direct call to emergency medical services on time delays and management of patients with acute myocardial infarction

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Background: Delayed access to medical care in patients with acute myocardial infarction (AMI) increases myocardial damage. Only few studies have analysed the influence of direct call to emergency medical services (EMS) in patients with AMI. From the regional observatory of MI (RICO) data base, we report the acute management in patients calling either EMS or other medical contact (OMC) as first medical seek after symptoms onset of MI.
Methods: Data were prospectively collected from January to October 2001, in the 6 medical units in charge of MI in the region of Côte-d'Or. Among the 322 patients included, only 57 (18%) directly called EMS after symptoms onset (group EMS) and 265 (82%) called another medical contact (group OMC).
Results: The baseline characteristics including age and risk factors were similar among the 2 groups of patients. Moreover, cardiovascular history was the same between the two groups, except for history of MI (21% in EMS group vs 11% in OMC group, $p<0.05$). The median times from symptoms onset to first medical intervention (48 vs 105 min, $p<0.02$) and from first medical intervention to hospital admission (60 vs 103 min, $p<0.02$) were markedly shorter in EMS group. We also observed a significant increase in reperfusion therapy at the acute phase in EMS group compared to OMC group (respectively 70% vs 48%, $p<0.003$), mainly due to a higher rate of primary angioplasty (respectively 33% vs 20%, $p<0.04$).
Conclusion: Our study in real world collecting data from a French regional population demonstrated that only a small rate of patients use the direct call to EMS at symptoms onset of MI. This study also documents the beneficial effect of a direct call to EMS by reducing the pre-hospital delays and by increasing the rate of early revascularisation.

P626 Sex differences in the treatment and outcome of acute myocardial infarction in an unselected population: data from the AMI-Florence registry

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Background: A higher mortality for women vs men with acute myocardial infarction (AMI) was reported in previous studies. However, scanty data exists about differences between males (M) and females (F) in the treatment strategy and outcome of AMI in an unselected population.
Methods: Data are derived from the AMI – Florence Registry, a prospective observational registry including all the Florence area residents who experienced ST-segment elevation AMI from March 1, 2000 to February 28, 2001 and were admitted to hospital within 24 h from symptom onset.
Results: Out of 806 pts included, 557 (69%) were M and 249 (31%) F. Mean age was 67±13 in M and 76±11 in F ($p<.000$). F had a higher prevalence of hypertension (62% vs 45%, $p<.000$), a less frequent habit of smoking (16% vs 35%, $p<.000$), a lower rate of previous revascularization (2.4 vs 8.4%, $p<.001$) and a higher rate of Killip class >1 at admission (36.9% vs 11.5%, $p=.001$). Median time from symptom onset to hospital admission was 135 min in M and 159 min in F(p=ns). Reperfusion treatment (RT) was used in 63% of M (primary percutaneous transluminal coronary angioplasty (P-PTCA) in 93%) and in 55% of F (P-PTCA in 93%) (p=ns). Median door-to-balloon time was not different between M (40 min) and F (45 min). Similar rates of stenting were observed in M (96%) and F (96%) while abciximab use was higher in M (66% vs 50%, $p=.001$). LV dysfunction (EF <50%) was observed at discharge in 77% of M and 81% of F (p=ns). While in-hospital mortality was significantly higher in F (12.9% vs 8.1%, $p=.04$), 6-month mortality was not (16.5% vs 14.2%, P=ns). At multivariate analysis, after adjustment for age, hypertension, diabetes, history of angina or heart failure or ictus, Killip class, infarct location, use of RT, F showed a lower risk of 6-month mortality (OR 0.61, 95%CI 0.37-1.00).
Conclusion: Despite their more advanced age and higher risk profile, women with AMI show a similar outcome as men when P-PTCA is the preferred reperfusion strategy.

P627 Early revascularization improves 1-year survival in 14-day survivors of acute myocardial Infarction

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Background: Studies on the effect of early revascularization in acute coronary syndromes have conflicting results whether it improves survival or not. We investigated the association between revascularization performed within 14 days after an acute myocardial infarction (AMI) and 1-year mortality.
Methods: Prospective cohort study using data from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) on patients admitted to the coronary care units of 61 Swedish hospitals 1995-1998. Patients with first registry-recorded AMI who were younger than 80 years and who were alive at day 14, including 2375 who were revascularized within 14 days, and 17862 who were not. One-year mortality data were obtained from the Swedish National Cause of Death Register.
Results: At 1 year unadjusted mortality was 8.9% (1598 deaths) in the conservative group and 3.3% (78 deaths) in the early revascularization group. In Cox regression analysis adjusting for 43 confounding factors and propensity score for revascularization, early revascularization was associated with reduction in 1-year mortality (relative risk, 0.48; 95% confidence interval 0.35-0.66; $P<0.001$) in 14-days survivors of AMI. This reduction of mortality was similar among all subgroups based on age, sex, baseline characteristics, previous disease manifestations, and medications.
Conclusions: In daily clinical practise early revascularization in AMI patients is associated with substantially reduced 1-year mortality. Our study supports an early invasive strategy in AMI patients.

P628 Standard versus early discharge with transtelephonic electrocardiogram transmission after acute myocardial infarction: a prospective randomized study

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The duration of hospital stay after acute myocardial infarction (MI) has decreased over the last years. The aim of our prospective, randomized ongoing study was to compare 2 discharge strategies in acute MI: standard at day 10 (STAND) vs early discharge at day 5 (EARLY). In the EARLY group, Pts were followed by transtelephonic ECG (TT-ECG) transmission (Card Guard, Israël) from day 5 through day 10. Endpoints were: mortality, cardiac complications (reocclusion, arrythmias, cardiac failure) at day 10, 1 month and 1 year. Pts were randomized at day 3 after admission. Exclusion criteria were: severe cardiac complication within 3 days and/or comorbidity requiring prolonged hospitalization. In the EARLY group, Pts had systematic EKG transmission at day 6, 8 and 10. Non invasive ischemic tests and coronary interventions were left at the discretion of the physician and were not mandatory for inclusion. Results. During the study period (march 2000- december 2001), 444 Pts admitted for acute MI were screened, and 90 Pts (20%) were randomized. Reasons for non-inclusion were: severe cardiac complication (141 Pts), comorbidity (59 Pts), refusal (43 Pts), participation to an other protocol (52 Pts), follow-up impossible (59 Pts). Baseline characteristics were comparable between the 2 groups except for age (57±11 vs 64±14 years) and female gender (7% vs 22%) in the EARLY and STAND groups respectively. Use of fibrinolytics (26% vs 23%), rates of primary PTCA (40% vs 28%) were comparable in the EARLY and STAND group respectively. There were 3 complications between day 5 and day 10, both in the EARLY group (unstable angina, transient stroke, pulmonary edema). Diagnostic was confirmed by phone contact and EKG transmission. Hospital stay was reduced by 3.5 ± 1.4 days in the EARLY group. At one-month, there were 2 deaths in the EARLY group: suicide in one, septal defect in one detected on the planed discharged day and 2 Pts (one in each group) had recurrent MI. In the EARLY group, a satisfaction questionnaire showed that all Pts were satisfied by early discharge and reassured by TT-ECG facilities. Early discharge was associated with subsequent cost reduction at one month (1500 euros).
Conclusion: In selected Pts with uncomplicated acute MI and no severe comorbidity, early discharge is safe and cost/effective. The use of TT-EKG-transmission gives adjunct security to the early discharge.

P629 Treatment and outcome of women and men with acute myocardial infarction: results from the Berlin myocardial infarction registry

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Introduction: Major Studies suggest, that women with acute myocardial infarction are treated less invasiv resulting in a reduced survival rate. The goal of our study was to evaluate gender specific differences in treatment and outcome of women and men with acute myocardial infarction in Berlin, Germany.
Methods and results: In the years 1999 and 2000 in 25 Berlin hospitals data from 3436 patients (35,7% f, 64,3% m) suffering from acute myocardial infarction was prospectivly collected. Mean age was 72,0 (f, ± 12,3) and 61,6 (m, ± 12,2) years. Time between myocardial infarction and hospital admission (median values) were 2.75h (f) and 2.25h (m) ($p<0,05$, U-test). Thrombolysis without catheter intervention was performed in 252 women (22,4%) and 523 men (26,15%). Acute catheter intervention without thrombolysis was performed in 218 women (19,3%) and 586 men (29,3%). A combined treatment (thormbolysis and acute PTCA) was performed in 55 women (4,9%) and 193 men (9,7%). After adjusting for the covariables (age, diabetes mellitus, arterial hypertension, former myocardial infarction, heart failure, localisation (anterior wall)) no significant difference was found between women and men regrading the frequency of PTCA and thrombolysis. No attempt to open the infarct related artery was performed in 602 women (53%) and 698 men (35%). In hospital 225 women (19%) and 187 men (8.8%) died. After adjusting for the fomer mentioned covariables this difference was non significant (OR=1,2; 95%CI 0,9-1,6).
Conclusion: After adjusting for the covariables women and men suffering from acute myocardial infarction (Berlin, Germany; years 1999 and 2000) don't show a difference regarding frequency of thrombolysis/PTCA and in hospital death ($p>0,05$).

P630 The prognosis after acute myocardial infarction continues to improve in the city of Göteborg, Sweden

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Background and aim of study: New knowledge has formed new treatment strategies for patients with acute myocardial infarction (AMI). We wanted to study how this has affected the short and long term prognosis for infarct patients, and discribe the development of coronary heart disease (CHD) mortality in our community.
Methods: Patients aged below 75 years hospitalized in Goteborg for AMI during 1990-91 (period I) and 1995-96 (period II) were compared in terms of previous history, treatment for AMI and outcome during hospitalisation and three years of follow-up. Information on CHD mortality in the community was gathered from the National Registry of Deaths.
Results: The number of patients were 921 in period I and 861 in period II, corresponding to an incidence of 200 and 183 per 100 000 inhabitants, respectively. During period II there was an increase in the use of PTCA, coronary by pass surgery, ACE inhibitors, heparins and intravenous nitroglycerine. On the other hand there was a decrease in the use of thrombolysis, diuretics, digitalis, longacting nitrates, calcium blockers and lidocaine. The inhospital mortality declined from 9.4% in period I to 6.0% in period II ($p=0.01$), risk ratio 0.65 (95% CI 0.45-0.94). The mortality over three years was 26.5% for period I patients and 17.8% for period II patients ($p<0.0001$), risk ratio 0.67 (95% CI 0.54-0.82). The CHD mortality in Goteborg declined from 1990 to 1995 in the age interval 30-74 years: age adjusted odds ratio 0.79 (95% CI 0.68-0.92).
Conclusion: The prognosis of AMI patients in Goteborg improved from 1990 to 1995, both during hospitalisation and during three years of follow-up. During the same time period the CHD mortality declined in the community of Goteborg.

P631 Prognostic value of consecutive abnormal signal-averaged electrocardiograms in patients after acute myocardial infarction

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Objectives: To assess the prognostic ability of consecutive abnormal signal-averaged electrocardiograms (SAECGs) during hospitalization after an acute myocardial infarction (AMI).
Methods: Seven hundred and five pts (525 men), aged 63±0.4 (SE) years in sinus rythm were studied prospectively post AMI. All pts underwent 1) Estimation of functional Killip class on admission, 2) SAECG obtained at the 1st, 3rd and 7th days after admission. Abnormal SAECG was defined if fQRS>114 ms plus either LAS>38 msec or RMS<20 μV for a standard QRS duration <120 msec or fQRS>155 msec, LAS>55 msec or RMS<17 μV for a standard QRS>120 msec. 3) Measurement of ejection fraction (EF) by 2D-echo on 1st day. 4) 24-hour Holter ECG recording with arrhythmias analysis based on Lown's classifications. 5) 12-lead ECG estimation of infarct size by QRS score based on Q and R wave duration and R/S and R/Q ratio before hospital discharge. Thrombolysis was given in 58% of pts. A cohort of 60 pts had consecutive abnormal SAECG.
Results: During a follow-up period of 39±0.9 months 178 (25%) pts died of cardiac causes (including sudden cardiac death). The presence of the 3 consecutive abnormal SAECGs was correlated with age ($p=0.00$), EF ($p=0.00$), old MI ($p=0.05$), anterior AMI (0.00), QRS score (0.00) and Killip class>II ($p=0.00$). In multivariate analysis (logistic regression) only age ($p=0.001$), EF ($p=0.002$) and abnormal consecutive SECGs ($p=0.00$) were independent predictors of cardiac mortality. The presence of 3 consecutive abnormal SAECG had higher specificity and higher positive predictive value (96% and 65%) than the separate abnormal SAECG (89% and 52% for the 1st, 90% and 42% for the 3rd or 87% and 32% for the 7th day respectively).
Conclusion: The presence of consecutive abnormal SAECGs improved the independent prognostic value of the SAECG for cardiac mortality.

P632 The influence of preinfarction angina on intrahospital mortality in patients with acute myocardial infarction

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In randomized trials it was found that patients (pt) with acute myocardial infarction (AMI) who had preinfarction angina (preAP) had a lower mortality compared to pt without preAP. This has not yet been shown in clinical practice.
Methods: From 5/96 to 01/01 we enrolled 20037 consecutive pt (age median 68 years; 34,5% female) with AMI in the German multicenter registries MIR-1, MIR-2 and MITRA-2 in whom in 18926 preAP was registered. We examined the influence of preAP on intrahospital mortality. PreAP was defined as instable angina pectoris which occurred up to 4 weeks before an AMI.
Results: (see table comparison of pt with and without preAP)
Prehospital delay in pt with preAP was 75 min longer compared to pt without preAP. Pt with preAP were 40% less often resuscitated and had about 30% less often a cardiogenic shock compared to pt without preAP. Hospital mortality in pt with preAP was significantly lower compared to pt without preAP.

Comparison of pt with and without preAP

	Pt with preAP (n=11483; 61%)	Pt without preAP (n=7443; 39%)	P value
Prehospital delay (min)	225	150	<0.001
Resuscitation	550 (4.8%)	602 (8.1%)	<0.001
Cardiogenic shock	470 (4.1%)	452 (6.1%)	<0.001
Hospital mortality	1563 (13.6%)	1096 (14.7%)	0.03

Conclusion: Almost 2/3 of all pt with AMI had preAP. Pt with preAP had a longer prehospital delay ($p<0.001$), they were less often resuscitated ($p<0.001$) and had less often a cardiogenic shock ($p<0.001$). In clinical practice hospital mortality in pt with preAP is little lower compared to pt without preAP ($p=0.03$).

P633 In-hospital and one-year outcomes of older high-risk patients with acute myocardial infarction treated with or without reperfusion therapy: data from the MISTRAL study

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Background: In spite of reduction of mortality for coronary heart disease in the last few years, the prognosis of older patients (pts) with acute myocardial infarction (AMI) still remains significantly unfavourable. Aim of this study was to assess the outcomes of older patients with high risk AMI in a large unselected Italian cohort of patients treated with or without reperfusion therapy (RT). Methods and results: 2227 HR-pts with ST-elevation AMI <12h were recruited at 17 centres with, and 30 without, feasibility of performing primary PCI (classified at HR having ≥1 of the following characteristics: female >70 y, diabetic >70 y, Killip class >1, SBP <100 mmHg and HR >100 b/m, >4 leads with ST deviation, previous Q-wave MI, contraindication to TT [10.2%]). 1747 pts (78.4%) were aged ≤75 years and 480 pts (21.6%) were older; older pts were more frequent females, presented a higher percentage of previous AMI, angina and history of heart failure and stroke, cardiac shock and acute heart failure at the entry and during hospital stay; they usually arrived later in hospital. Older patients were undertreated with RT (primary-PCI and thrombolysis) respect to younger ones (38.5% vs 13.2%, $p<0.0001$) and with life-saving therapy such as beta-blockers and ACE-inhibitors in hospital and during follow-up. In hospital mortality and combined end-point (death+reinfarction+stroke) rates were higher in older pts with respect to younger ones (26.2% vs 5.8%, $p<0.0001$; 28.1% vs 7.8%, $p<0.0001$, respectively). At 1-year we found that older pts still maintained a significant poor prognosis (death: 42.6% vs 10.6%, $p<0.0001$; death+reinfarction+heart failure+angina: 55.2% vs 29.8%, $p<0.0001$). Adjusting for clinical and haemodynamic parameters, older pts presented a higher mortality and combined end-point at 1-year rates (OR 4.21, 95%CI 3.15-5.62; OR 2.03 95%CI 1.60-2.58 respectively).
Conclusion: Advanced age is an independent predictor of prognosis independently of clinical and haemodynamic profile of high risk patient with AMI. Older patients seem to be excluded by aggressive therapy of AMI. To reduce their elevated mortality new methods for increasing the use of reperfusion therapy in this subgroup of patients should be planned.

P634 Prognostic importance of rest electrocardiogram for a large population of coronary care unit-patients (CCU): a one year follow-up

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Background: The aim of this study was to investigate the prognostic importance of an admission-ECG, on in-hospital and 1-year mortality.
Methods: The Swedish Register of Cardiac Intensive Care (RIKS-HIA) contains data collected on case record forms including 100 variables for each patient. A total of 167302 patients with chest pain as the cause of CCU-admission were divided, from an admission standard ECG taken at rest, into eight ECG-groups; normal ECG, ST-depression (STD), ST-elevation (STE), new Q-wave, left bundle branch block (LBBB), T-inversion, old Q-wave and other pathology. Study end points, in-hospital and 1-year-mortality, were studied by merging the RIKS-HIA database with The National Cause of Death-register. Multiple covariate Cox-regression analysis was used to identify any variable with a significant influence on mortality.
Results: Patients with abnormal ECG findings were older and risk factors were more common compared to the normal ECG-group ($p<.001$). The proportion of previous heart disease was significantly higher in the abnormal ECG-groups compared to normal ECG, with some exceptions for STE and new Q-wave groups. The normal ECG-group had the lowest in-hospital and 1-year mortality (0.7 and 3.5%). New Q-wave and STE had the highest incidence of in-hospital mortality (12.2 and 8.5% respectively), though all abnormal ECG-groups showed significantly ($p<.001$) higher mortality than normal ECG. 1-year mortality was high for new Q-wave (19.9%) and STE (15.6%) but compared to in-hospital mortality the incidence was increasing more for LBBB (6.6 to 22.0%), STD (4.5 to 15.7%) and other pathology (5.1 to 14.7%). Relative ratios for 1-year mortality using multiple covariate Cox-regression were for normal ECG 1.0, T-inversions 1.47, old Q-wave 1.58, other pathology 2.22, STD 2.25, LBBB 2.53, STE 2.97 and new Q-wave 3.32.
Conclusion: A first rest-ECG in patients with chest pain can be used as a prognostic instrument for 1-year mortality. A normal ECG is predictive of a good prognosis whereas LBBB, new Q-wave, STE and STD had the highest mortality during follow-up.

PLATELET FUNCTION AND BIOCHEMISTRY

P635 Platelet expression of GP IIb/IIIa and P-selectin and its relation to platelet aggregation early after percuteneous coronary intervention (PCI)

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Background: Platelets are key elements in early thrombotic events following PCI. Besides platelet-platelet aggregation, signalling transduction in activated platelets lead to expression of adhesion molecules on its surface and release of coagulation factors from platelet granules. Herein, we souhgt to determine the relation between fibrinogen binding to activated GPIIb/IIIa and P-selectin surface expression and platelet aggregation following PCI.
Methods: Blood samples from 32 consecutive pts were obtained before and at 1, 4, and 24 hours after coronary stenting. Platelet activation was assessed by measuring GPIIb/IIIa (anti-human fibrinogen FTIC) fibrinogen binding and P-selectin (CD62-PE) surface expression in stimulated platelets (2μM ADP) using whole blood cytometry. Platelet aggregation was measured using light transmittance aggregometry with 6 μM ADP as agonist. Pts were divided into 2 groups according to GPIIb/IIIa receptor fibrinogen binding. Pts having a percentage of fibrinogen positive platelets in 3 or more samples (baseline, 1, 4, 24h) above or below the median were considered as having high (group H, n=15 pts; 12 males, age 64 ±9y) or low (group L, n=17 pts; 16 males, age 61±11y) platelet activation. All pts were on aspirin treatment (100mg/day) and received 300 mg clopidogrel loading-dose at procedure time. Pts receiving GPIIb/IIIa inhibitors were excluded.
Results (mean±SD): Platelet aggregation was significantly higher in group H than L, at 1 hour (58±14% vs 46±18%; p=0.04) and 4 hours after PCI (46±17% vs 33±16%; p=0.04). P-selectin expression was higher in group H at 4 hours (29±11% vs 17±7%; p= 0.003) but not at 1hour (38±16% vs 29±13%; p= 0.1) following PCI. After 24hours, a trend towards higher P-selectin expression (31±15% vs 18±12%; p=0.2) and less platelet inhibition (40±24% vs 26±16%; p=0.07) was found in group H compared to group L. No difference in platelet count was observed between the two groups.
Conclusions: Pts having an increased GPIIb/IIIa activation following PCI have, in addition to less inhibition of platelet aggregation, an enhanced platelet surface P-selectin expression. These data suggest that antiplatelet therapy other than GP IIb/IIIa receptor antagonist may be necessary to improve clinical outcome following coronary interventions.

P636 Prevalence of HPA-2 and VNTR platelet glycoprotein Ib a polymorphisms in patients with angiographically documented coronary artery disease

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Platelet GP Ib-IX-V complex receptors play a key role in primary haemostasis and in the development and progression of obstructive coronary artery disease (CAD). Two polymorphisms of GP Iba are hypothesised to facilitate platelet adhesion and therefore increasing thrombotic risk. Our objective was to investigate their prevalence in a case-control study in patients with angiographic documentation of CAD.We studied 690 patients(pts) referred to the Catheterization Laboratory for coronary angiography (mean age 61 ± 10 years, 67,5% males). Diagnoses: heart valve disease in 15,5%, acute coronary syndromes in 26,2% and stable angina in 58,3% of pts. HPA-2 and VNTR genotype were identified by polymerase chain reaction (PCR)/enzymatic restriction and PCR/direct electrophoresis. Statistical analysis was performed with SPSS software. Discrete variables were compared with x2 test and continuous variables were compared with Student t test. Odds ratios and confidence intervals (CI) were calculated. Cases were 386 pts (55,9%) with coronary artery disease (CAD +) and controls were 304 pts (44,1%) without coronary artery disease (CAD -). Pts with CAD were older (62 ± 10 vs. 60 ± 10 years; p= 0,03) and more frequently male (79% vs. 21%, p=0,0001). The frequencies of HPA, VNTR genotypes and prothrombotic alleles (b of HPA-2 and B of VNTR) were not statistically different between cases and controls (table).

	HPA-2			VNTR					
	a/a	a/b	b/b	B/C	C/C	C/D	D/D	B/D	B/B
CAD+	75,6	23,3	1	20,5	63,5	10,6	2,3	2,1	1
CAD-	79,6	19,7	0,7	18,1	67,4	10,5	1	2	1
p value		0,4					0,7		
alleles(%)	a	b		No B	B				
CAD+	75,6	24,4		76,4	23,6				
CAD-	79,6	20,4		78,9	21,1				
p value	0,2			0,4					
Odds Ratio(95%CI)	0,79(0,55-1,14)			0,86(0,6-1,24)					

Genotype and allele frequencies of HPA-2 and VNTR polymorphisms

These results were similar in patients younger and older than 60 years. We concluded that the presence of HPA-2 or VNTR polymorphisms did not increased the risk of angiographically documented coronary disease in this population.

P637 Platelet GP IIb/IIIa and non-receptor tyrosine kinases pp60 c-src and pp125FAK in patients with advanced pulmonary hypertension

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Altered platelet function has been reported in pulmonary hypertension (PH) with "exausted" platelets being detected in some instances. In view of the central role played by glycoprotein IIb/IIIa (GP IIb/IIIa) in platelet physiology, we decided to analyze the behaviour of GPIIb/IIIa and two important signalling molecules, pp60c-src and pp125FAK in four adult patients with advanced PH in whom decreased platelet aggregation was observed. Platelets were analyzed at rest and following thrombin-stimulation. Platelet cytoskeleton was analyzed as the Triton-insoluble fraction. Proteins were semiquantified by densitometric analysis of luminographs after Western immunoblotting. Total platelet GP IIb/IIIa and its attachment to platelet cytoskeleton following stimulation was 40% decreased in patients in comparison with normals. This was associated with a 30% reduction in phosphorylated pp125FAK (P-pp125FAK) in comparison with controls following thrombin-stimulation, although total platelet pp125FAK was not decreased. In patients, platelet levels of pp60c-src and phosphorylated pp60c-src (P-pp60c-src) were close to normal at rest and following stimulation. P-pp60c-src increased approximately 45% after stimulation in both groups. Platelet pp60c-src phosphorylation was an activation-independent phenomenon, with considerable amounts of P-pp60c-src being present in resting platelets in patients and controls. In contrast, negligible amounts of P-pp125FAK were present in unstimulated platelets. Our findings suggest that altered platelet function in these patients was partly due to abnormal content and physiology of GPIIb/IIIa. In particular, since pp125FAK phosphorylation is a GPIIb/IIIa-mediated phenomenon, reduced platelet GPIIb/IIIa may have accounted for reduced levels of P-pp125FAK following thrombin stimulation.

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P638 Transient coronary occlusion stimulates microvascular platelet deposition in remote myocardium

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Acute coronary syndromes are associated with activation of circulating platelets and with the development of a systemic inflammatory response. These phenomena may lead to increased endothelial adhesiveness and thrombogenicity of the macro and microvasculature in remote territories, with potential adverse consequences. In the present study, we aimed to investigate the magnitude of microvascular platelet deposition in a remote myocardial region after a transient coronary occlusion, and its association with the thrombotic activity at the culprit lesion and with the severity of myocardial damage in the reperfused zone.

Methods: Nine thiopental-anesthetized, open-chest pigs (34 ± 2 kg), in which platelets had been labeled with 99mTc and re-injected on the previous day, were submitted to catheter-induced mechanical injury of the left anterior descending coronary artery (LAD) followed by a 48-min ligation and two hours of reflow. Then, the heart was excised and the aortic root perfused for several minutes to wash the coronary vasculature. Myocardial platelet content was assessed by gamma counting of samples (3.6 ± 0.1 g) from reperfused myocardium and from myocardium supplied by the right coronary artery. Neutrophil content was quantified by measuring the myeloperoxidase (MPO) activity, and infarct size by triphenyltetrazolium chloride staining.

Results: Animals had 10 ± 3 cyclic flow reductions in the LAD during the reperfusion period. Platelet content (x107/g) in the control and ischemic zones averaged 1.42 ± 0.16 and 4.27 ± 0.93, respectively (P=0.008), MPO activity was 0.13 ± 0.05 and 0.25 ± 0.07 U/g, respectively (P=0.07), and infarct size averaged 5.6 ± 1.2% of ventricular mass. Platelet content in the control region was not associated with the number of cyclic flow reductions in the LAD, but was correlated with platelet content (r=0.74, P=0.02) and MPO activity (r=0.56, P=0.12) in reperfused myocardium, as well as with infarct size (r=0.72, P=0.03). Thus, the results suggest that transient coronary occlusion stimulates an active microvascular platelet deposition in remote myocardium, whose magnitude correlates with the severity of ischemic injury.

P639 Abnormal platelet Na^+/H^+ exchanger activity in patients with cardiac syndrome X is not associated with platelet activation in vivo

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An enhanced activity of the Na^+/H^+ countertransport has previously been suggested in red blood cells of patients with syndrome X (SX). In this study we investigated whether the activity of the Na^+/H^+ exchanger (NHE) is also increased in platelets of SX patients and whether this abnormality is associated with platelet activation in vivo.

The activity of platelet NHE was evaluated in 21 SX patients (12 women, 9 men; age 59±7 years)and in 18 matched controls (8 women, 10 men; age 54±5 years) by measuring the rate of cytoplasmic pH recovery of BCECF-loaded platelets in response to different degrees of acid loading, obtained by platelet exposure to increasing sodium propionate concentrations. A significant linear correlation between the intracytoplasmic pH value reached with increasing cytoplasm acidification (pHi) and the maximal velocity of platelet pH recovery (Delta-pHi, which reflects NHE activity) was found in all subjects of both groups. The slope of the regression curve and the Delta-pHi value intercept at pHi=6.6 on the regression curve were calculated for each patient and control by linear regression analysis. Delta-pHi in response to increasing acid loading resulted significantly higher in SX patients, compared to controls (0.75±0.29 vs. 0.5±0.23, respectively, p=0.01); accordingly, the intercept Delta-pHi value at pH=6.6 was also significantly increased in SX patients (0.24±0.1 vs. 0.17±0.1 in patients and control, respectively, $p<0.05$). There was no evidence of increased platelet activation in vivo in SX patients, since no significant difference was observed in 24-hour urinary 11-dehydro-TXB2 excretion between patients (median 920 pg/mg creatinine, range 358-3625, n=15) and controls (median 765 pg/mg creatinine, range 498-1175, n=15) (Mann-Whitney, p=0.32, NS).

Thus, our data show increased platelet NHE activity in response to acid loading in SX patients, suggesting a possible role of NHE abnormalities in the pathophysiology of this syndrome. The increased platelet NHE, however, did not seem to be associated with platelet activation in vivo.

P640 Persistent increased of sympathetic tone after thrombolysis is associated with angiographic no-reflow phenomenon

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Background: Prolonged ischemic injury evokes sympathetic reflexes that result in alpha-adrenergic microvascular constriction. We assessed the hypothesis that changes in autonomic nervous system activity may contribute to the no-reflow phenomenon following thrombolysis (TL).
Methods: We studied 59 pts with diagnosis of acute myocardial infarction, admitted to CCU, and treated with medical therapy (including beta-blockers) and systemic TL (rt-PA) within 6 hrs from the onset of symptoms. At admission pts underwent 24 hrs ECG-Holter monitoring for evaluating frequency domain measures of heart rate variability. Measurements were done before TL (T1), and 30 minutes (T2) and 24 hours (T3) after TL. Low (LF: 0.04-0.15) and high frequencies (HF: 0.15-0.40) were assumed to be the expression of sympathetic and parasympathetic activity, respectively. LF/HF ratio was used to estimate the overall autonomic nervous system balance. Clinical correlates of successful reperfusion were considered the occurrence of >50% reduction of ST segment elevation within 90 minutes and/or a CK-MB peak within 12 hours from the onset of TL. Pts performed diagnostic coronary angiography within 7 days from admission.
Results: 49/59 pts showed clinical signs of reperfusion. At angiography they were found to have a TIMI flow grade 3 in the infarct related artery (G1). The remaining 10 pts did not show clinical signs of reperfusion. Angiography showed a TIMI flow grade 1-2 (G2). Residual coronary stenosis following TL were comparable in G1 and G2. At T1, LF/HF ratio was not significantly different in G1 and G2 (5.6 ± 2.7 and 5.4 ± 2.9, respectively). At T2, LF/HF was dramatically increased (sympathetic activation) in G1 and G2 pts (9.2 ± 1.7 and 12.1 ± 2.7, respectively; $p < 0.001$). At T3 LF/HF was still high in G2 but not in G1 (7.5 ± 1.2 vs 1.9 ± 1.1; $p < 0.001$).
Conclusions: (1) Persistent increased of sympathetic tone after TL is associated with angiographic no-reflow phenomenon (TIMI flow grade 1- 2) of the infarct related coronary artery. (2) Cardiocardiac sympathetic reflexes may result in alpha-adrenergic microvascular constriction, which may contribute to no-reflow phenomenon after TL. (3) Alpha-adrenergic blockers might be beneficial in improving coronary blood flow following acute myocardial infarction.

P641 Regulation of local fibrinolytic activity in vivo in man

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Background: Tissue-type plasminogen activator (tPA) is the key enzyme of the endogenous fibrinolysis. The endothelium is the main source of tPA in plasma and stimulation of its release may be a physiologic counter-regulatory mechanism to prevent formation of occlusive intraluminal thrombi. However, free active tPA is rapidly inactivated by plasminogen activator inhibitor-1 (PAI-1), which is found in molar excess in plasma. We now investigated in a large invasive study how the local availability of free active tPA is regulated during basal and stimulated conditions.
Methods: Ninety-six healthy subjects participated in an invasive perfused-forearm study. Local release of fibrinolytic proteins was assessed by arteriovenous concentration gradients and plasma flow, at baseline and during stimulation by sodium nitroprussid (SNP; 10 μg/mL/min), methacholine chloride (Mch; 4 μg/mL/min), and desmopressin (DDAVP; 70 ng/mL/min).
Results: In the morning there was a low-rate continuous secretion of tPA antigen in the order of 80 fmol/min/L tissue. At noon, tPA release had increased by 45% and the free tPA fraction rose 3-fold. In spite of a 5 to 10-fold molar excess of the arterial input of active PAI-1, between 34% and 72% of the released tPA remained in its free active form. Stimulation by SNP, Mch, and DDAVP induced a 3 ($p=0.04$), 6 ($p<0.0001$), and 12-fold ($p<0.0001$) increase in local tPA release, respectively. Again, despite a large arterial supply of PAI-1, a even greater proportion of the released tPA appeared in the free tPA fraction which increased 5.5 ($p=0.01$), 8.5 ($p<0.01$), and 18-fold ($p<0.0001$), respectively. The correlation between the total tPA release and increments in free tPA became stronger as the release rate of tPA increased ($r=0.38$, $p<0.05$ to $r=0.85$, $p<0.001$), indicating that total tPA was the major determinant of free tPA production, while PAI-1 input had a diminutive influence on the availability of free tPA.
Conclusion: During high release rate of tPA from the vascular endothelium the free active fraction of tPA increases profoundly and tPA is not inactivated despite a several-fold molar excess of PAI-1. Thus, the magnitude of the activation of the local fibrinolytic system in response to stimulation is mainly determined by the capability for tPA release and not the level of circulating PAI-1.

P642 Effect of delapril-manidipine combination versus irbesartan-hydrochlorothiazide combination on fibrinolysis in hypertensive diabetic patients

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Aim: to compare the effect of delapril-manidipine combination vs irbesartan-hydrochlorothiazide combination on plasma tissue plasminogen activator (t-PA) and inhibitor 1 (PAI-1) activity in hypertensive type 2 diabetic patients.
Methods: after a 4 weeks placebo run-in period 80 hypertensive patients (DBP ≥ 95 ≤ 105 mm Hg) with well controlled type 2 diabetes were randomized to delapril 30 mg o.d. or irbesartan 150 mg o.d. for 8 weeks: then manidipine 10 mg o.d. was added to delapril and hydrochlorothiazide 12,5 mg o.d. was added to irbesartan for further 8 weeks. The last day of the placebo run-in period, of the monotherapy period and of combination therapy period blood pressure was measured and a blood sample was taken to evaluate plasma PAI-1 and t-PA activity (at the same hour in the morning).
Results: the results of the study are shown in the table.

	Placebo	Delapril	Delapril + Manidipine	Placebo	Irbesartan	Irbesartan + HCTZ
SBP (mmHg)	161.9	144.5**	131.9***	160.8	144.8**	132.3***
DBP (mmHg)	101.8	88.8**	80.0***	100.9	90.1**	81.5***
PAI-1 (IU/ml)	25.5	15.4*	14.9*	26.1	30.4	33.2
t-PA (IU/ml)	0.49	0.50	0.8*	0.47	0.46	0.30*

* $p < 0.05$ ** $p < 0,01$ *** $p<0,001$ vs placeboHCTZ = hydrochlorothiazide

Conclusion: these results suggest that in patients with imparied fibrinolysis an ACE inhibitor - Ca antagonist combination could improve the fibrinolytic balance more than the single drugs and more than an Angio II antagonist – hydrochlorothiazide combination. It represents a further indication to the use of ACE inhibitor - Ca antagonist combinations in hypertensive diabetic patients, where it is diffcult to reach the required blood pressure target with a single drug.

P643 Differential regulation of plasminogen activator inhibitor type 1 expression by statins in human vascular smooth muscle cells

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Background: Plasminogen activator inhibitor type 1 (PAI-1) has been established as an independent risk factor for cardiovascular disease. HMG CoA reductase inhibitors are known to induce other beneficial effects besides inhibiting synthesis of cholesterol. So far, no comparison of all clinically used statins with respect to their ability to modulate pathologically increased PAI-1 expression has been reported. Therefore, this study was designed to characterize potential statin-mediated modulation of PAI-1 synthesis in human vascular smooth muscle cells (HVSMC) known to play a pivotal role in atherogenesis.
Methods: HVSMC (passages 4-7) from healthy donors were exposed to selected concentrations (0, 0.1, 1, and 10 μM) of statins in the presence or absence of 1 ng/ml TGF-β known to be involved in atherogenesis and to be one of the most potent agonists of PAI-1 expression. PAI-1 protein concentration in conditioned media was quantified by ELISA, PAI-1 gene expression by Northern blotting.
Results: After 24 h, PAI-1 protein concentration decreased by up to 12% with pravastatin (p=ns), 37% with simvastatin ($p=0.018$), 39% with lovastatin ($p=0.003$), 44% with atorvastatin ($p=0.003$), 46% with fluvastatin ($p=0.014$), and 50% with cerivastatin ($p=0.027$) in the presence of TGF-β (each n=9), concomitantly with decreased PAI-1 gene expression (n=3). In contrast, under basal conditions PAI-1 expression was not significantly affected by statins. Total protein concentration was not altered in either case. In time-course experiments (4, 12, 24, 48, and 72 h), the inhibitory effect of statins increased over time and was maximal at 72 h (n=3).
Conclusion: Thus, the clinically used statins differ substantially in their ability to reduce pathologically increased PAI-1 expression. By selecting specific statins and by developing corresponding derivatives the beneficial effect of statins in cardiovascular disease may be potentiated in patients with concomitantly increased PAI-1 expression.

COMPUTERS IN CARDIOLOGY

P644 Unjustified prehospital fibrinolytic therapy using different means of electrocardiogram diagnosis of myocardial infarction

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Background: Two cities in The Netherlands, Rotterdam and Nijmegen, have a well organised prehospital fibrinolytic therapy (FT) program for acute myocardial infarction (MI). Reports in the literature give an estimation of 5-10% of patients receiving fibrinolysis without having MI, but none differentiate between aborted MI (dynamic ECG criteria, no rise of cardiac enzymes), acute coronary syndrome (ACS) and unjustified treatment. We studied the incidence of unjustified FT using different ways of diagnosing MI in prehospital settings, and compared the results with in-hospital treated patients (Arnhem).
Methods: In Nijmegen ECG's of patients with chest pain are made by the ambulance staff, and transmitted to the CCU using a transtelephonic data transmission system. The diagnosis is confirmed by the attending cardiologist, if more than 0.6 mV of ST-elevation is seen. In Rotterdam acute MI is confirmed if more than 0.3 mV ST-elevation in at least more than 2 precordial leads or more than 0.4 mV ST-elevation in at least more than 2 extremity leads are measured by a mobile computer system. Unjustified FT was retrospectively assessed if there was no rise in cardiac enzymes and a diagnosis of aborted MI or ACS could be ruled out.
Results: (table). In-hospital therapy does not differ in unjustified FT compared to prehospital FT (p=0.33).

Unjustified FT

	patients	unjustified FT	mean ST-elevation
Rotterdam	118	2 (1.7%)	0.96 mV
Nijmegen	132	2 (1.5%)	1.20 mV
Arnhem	269	1 (0.4%)	0.84 mV

Prehospital (Rotterdam & Nijmegen)and in-hospital (Arnhem) strategy, and unjustified FT

Conclusion: Computer and cardiologist assisted ECG diagnosis of MI result in a similar incidence of unjustified FT and does not differ significantly from in-hospital FT. Our data support the use of simple computer diagnosis of MI leading to a further shortening of delay.

P645 The problems of evaluating computer-based analysis of paediatric electrocardiograms

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Introduction: Computer analysis of paediatric ECGs is a relatively neglected area. There are few paediatric cardiologists skilled in ECG analysis and hence it is difficult to evaluate computer-assisted reporting techniques.
Aim: The aim of this study was to evaluate the performance of the Glasgow program in a paediatric population by comparing the computer interpretations of RVH and LVH with those of two paediatric cardiologists.
Methods: 984 ECGs were recorded on both inpatients and outpatients, ranging in age from the first day of life to 18 years. The cardiologists were given the 12-lead ECG traces together with the age and sex of the child with the computer interpretation and all other remaining information removed. In 671 ECGs, the clinical indication for the ECG was available and this was shown on the ECG; the remaining 313 ECGs had no further information available and were reported 'blind' without the clinical indication, e.g. atrial septal defect.

Sensitivity and specificity of program versus the cardiologists

	RVH				LVH			
Cardiologist	1		2		1		2	
Reported blind?	Yes	No	Yes	No	Yes	No	Yes	No
No. of cases	19	117	19	100	17	62	11	44
Sensitivity (%)	63.2	37.6	57.9	44.0	41.2	32.3	25.0	36.4
Specificity (%)	98.0	94.9	97.6	95.1	97.3	96.9	96.0	96.3

Results: The sensitivities and specificities of the program are shown in table 1. The cardiologists were designated '1' and '2' and the results subdivided according to whether or not ECGs were reported blind. 'RVH' and 'LVH' include definite, probable and possible hypertrophy. The performance of the program was markedly better when compared with the cardiologists reporting blind (except for LVH by cardiologist 2) than when the cardiologists were provided with the clinical indication. There were also differences between the two cardiologists which were most pronounced for the reporting of LVH blind.
Conclusion: The results of this study illustrate the difficulties in evaluating computer software. The sensitivity of the program varies from 37.6% to 63.2% for RVH and from 25.0% to 41.2% for LVH. The specificities are much more consistent (from 94.9% to 98.0% for RVH and from 96.0% to 97.3% for LVH).

P646 PRIME-ECG mapping in the diagnosis of acute myocardial infarction

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Introduction: In up to 50% of patients with acute coronary syndromes (ACS) the classical 12-lead ECG shows no pathological findings. Several other ECG modifications were developed to raise diagnostic sensitivity for coronary ischemia; e.g. in the 70s the principal of surface mapping. Recently, a fully automated system has been developed in order to make daily use and diagnostic easier. The aim of this study was to evaluate sensitivity and specificity of Prime-ECG in patients with acute coronary syndrome admitted to an emergency room.
Methods: We included 41 patients; 20 patients with proven acute myocardial infarction (defined as Tn-T positive and/or elevated CK values).
PRRIME-ECG recordings (BPSM-System; Meridian Medical Technologies) using a vest with 80 electrodes - including the classical 12-lead ECG - were taken at time of enrolment (time 0) and 3 and 6 hours thereafter (time 3/time 6) always simultaneous with analysis of CK and troponin T (Tn-T). The extent of the ischemic area was defined as the number of leads showing ST-segment deviations > +1mV or ≤ -0.5 mV if analysed according to manufacturers instructions.
Results: The results are shown in the table below (Se: Sensitivity/Sp: Specificity).

St-deviations	Positive Markers of Cardiac Ischemia (number n)	Negative Markers of Cardiac Ischemia (number n)
< +1mV	8	10 (Sp: 48%)
> + 1mV	12 (Se: 60%)	11
> -0.5 mV	7	8 (Sp: 38%)
< -0.5 mV	13 (Se: 65%)	13

Conclusions: In our series of patients admitted to an emergency room the PRIME-ECG exerted a low sensitivity and specificity in the diagnosis of acute myocardial infarction. With regards to the higher diagnostic costs and time demand the Prime-ECG seems to be less advantageous than biochemical markers for daily routine in an emergency room setting.

P647 Can "P"-wave wavelet analysis predict atrial fibrillation post CABG surgery?

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The aim of this study was to evaluate the predictive value of the P wave wavelet analysis for the development of postoperative atrial fibrillation (PAF) in CABG patients.
Methods: The P wave was analyzed using the Morlet wavelet in 37 patients who underwent successful CABG surgery. Group A consisted of 13 pts, mean age 67.2 ± 6.3, who developed post-CABG PAF and Group B consisted of 24 pts, mean age 63.2 ± 8.3, who remained arrhythmia free. Recordings using a 3-channel digital recorder (Galix Biomedical Instrumentation, Inc. USA) were obtained from all patients at resting conditions for 10 minutes. All ECGs were digitized with a sampling frequency of 1000Hz. Using a custom-made software wavelet parameters expressing the mean and peak energy of the P wave were calculated for each ECG orthogonal lead (X,Y,Z) and the vector magnitude (VM) at three frequency bands (200-160Hz, 150-100Hz and 90-50Hz). The P wave duration was also measured in these axes. Multiple regression analysis and the boot-strapping technique based on these parameters were used for the calculation of the pathologic cut-off point value. Sensitivity (Sn), specificity (Sp), positive and negative predictive value (PPV, NPV) were also calculated.
Results: The pathologic cut-off point value was calculated at –1.64. This led to a Sn 92.3%, Sp 87.5%, PPV 80% and NPV 95.4%.
Conclusion: The P wave Morlet wavelet analysis is a very sensitive and specific method in distinguishing patients who are going to develop atrial fibrillation after CABG surgery.

P648 Reconstruction of 12-lead electrocardiograms from reduced lead sets

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Background: In clinical practice, continuous recording of all leads of the 12-lead ECG is often not possible. We wanted to assess how well the 12-lead ECG can be reconstructed from a subset of leads and how well lead reconstruction performs over time.
Methods: Two sets of 12-lead ECGs were used, one consisting of 2372 10-second ECGs and the other consisting of 234 24-hour ECG recordings. These sets were divided in equally-sized training and test sets. Precordial leads were systematically removed, and for all lead subsets including both limb leads and at least one precordial lead, the missing leads were reconstructed using general and patient-specific reconstruction. Reconstruction performance was measured by correlation between the original and reconstructed leads, by average and maximum absolute ST-differences, and by agreement when a clinical decision rule was applied. Reconstruction performance over time was evaluated using the 24-hour recordings.
Results: Reconstruction accuracy was high (correlation >0.98, ST-difference <30μV, agreement >99%) with general reconstruction for lead sets with one or two precordial leads removed, but was less satisfactory when more leads were missing. Patient-specific reconstruction performed well when up to 4 precordial leads were removed (correlation >0.98, ST-difference <19μV, agreement >99%). When reconstruction coefficients derived from one set were applied to the other set, similar results were obtained. Patient-specific reconstruction performance initially slightly decreased and then stabilized over time, but remained much better than general reconstruction after 24 hours.
Conclusions: Accurate reconstruction of the 12-lead ECG from lead subsets is possible. General reconstruction allows reconstruction of 1 or 2 precordial leads, whereas up to 4 leads can be reconstructed well using patient-specific reconstruction.

P649 Wavelet based analysis of ventricular conduction in post infarction patients with and without ventricular tachycardia

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Wavelet analysis is a novel spectro-temporal technique which can reveal dynamic changes within each frequency band during the duration of the cardiac cycle length. The aim of this study is to identify if there are any differences in electrical conduction in post-myocardial infarction (PMI) patients with or without history of ventricular tachycardia (VT) using the Morlet wavelet analysis.
Methods: We studied the QRS interval based on the Morlet wavelet analysis in 22 PMI patients (Group A: 11 patients without history of VT, 8 males, mean age 65±6 years - Group B: 11 patients with history of VT, 9 males, mean age 64±5 years) and compared them with 11 normal individuals (Group C, 8 males, mean age 56±16 years). Recordings using a specially designed 3-channel digital recorder (Galix Biomedical Instrumentation, Inc. USA) in X, Y and Z-axes were obtained from all individuals at resting conditions for 10 minutes. All ECGs were digitized with a sampling frequency of 1000Hz. Using a custom-made software the mean and maximum energies in 3 frequency bands (200-160Hz, 150-100Hz and 90-50Hz) were calculated for the QRS complex in the three axes X, Y, Z and in the vector magnitude (VM).
Results: There were no differences in QRS duration between Group A patients and normal individuals. QRS complex was significantly prolonged in Y, Z and VM axes in Group B ($p<0,03$) compared to normals, and in Y axis compared to Group A. Wavelet analysis revealed decreased energy distribution in Z and VM axes for Group A and in Y, Z and VM axes for Group B compared to normals. These findings were similar in all frequency bands for both mean and max energies.
Conclusions: These findings suggest that PMI patients with VT display a different depolarization pattern compared with PMI patients without VT and normal individuals.

P650 The long-term ST database: reference for automated ischaemia detection systems and for studies of transient myocardial ischaemia

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The Long Term ST database is a result of multinational effort in the field of annotated electrocardiogram databases. The database is a research resource for development and evaluation of automated systems to detect transient ST segment changes in ambulatory electrocardiograms, and for physiologic studies of transient myocardial ischemia. Ambulatory records of the database were selected in routine clinical practice settings in the United States and Europe between 1994 and 2000. Records were pre-processed, heart beat reference points were determined manually, time series of diagnostic and morphologic feature were derived, and significant transient ST segment events were annotated.
Due to enormous amount of data, we used automated techniques as much as possible. Interactive graphic editor tools and automated techniques developed allowed to work paperless and facilitated international co-operation via the Internet.
The database contains two and three-channel 24-hour annotated ambulatory records from 80 patients (all together 86 records).
The database record files are in standard WFDB format to be consistent with the MIT-BIH, AHA, and the European Society of Cardiology ST-T databases.
The files contain detailed clinical information for the subjects, waveform data, true QRS annotations, ST segment annotations, and ST segment measurements obtained on average heart beats. The database records are stored on a DVD-ROM. The database is intended as a complement to the European Society of Cardiology ST-T database, and to the MIT-BIH and AHA databases. We wish to better represent the wide variety of "real-world" data, including long-term ambulatory records with many examples of transient ischemic and non-ischemic ST segment events while ST segment measurements were obtained on average waveforms, and to permit researchers to study physiologic mechanisms and dynamics of transient ischemia.

P651 Signal-adapted wavelet preprocessing for support vector machines for detection of ventricular tachycardia

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The use of morphology based detection criteria may enhance specificity of the detection of ventricular tachycardias (VT) in implantable cardioverter-defibrillators (ICD). The aim of the study was to compare the efficacy of a VT detection algorithm using a hybrid signal-adapted wavelet-support vector machine (SVM) to a detection scheme using correlation waveform analysis (CWA) with best fit alignment of bipolar right ventricular electrograms (EGM).
Methods: EGM were obtained during an electrophysiological study in 10 patients (pts) (mean age: 66 years, male: 81%, coronary artery disease: 86%, mean ejection fraction: 0.42) with inducible monomorphic VT. The filtered (10-500 Hz) and digitized (2 kHz, 12 bit) EGM were recorded during sinus rhythm (SR) and VT. 480 consecutive EGM (VT:240, SR:240) were analyzed. For each pt, 8 consecutive EGM during SR and VT were used for training of SVM. CWA and SVM were applied to the remaining 320 EGM.
Results: By using SVM, all arrhythmia episodes were classified correctly. By using CWA, VT could not be discriminated from SR in 4/10 pts (Fig. 1).

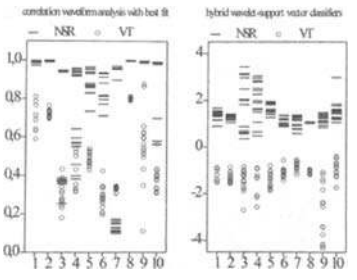

Fig. 1: CWA vs. SVM.

Conclusions: Analysis of EGM morphology in the wavelet-domain seems to be feasible for discrimination of SR from VT. This algorithm may contribute to an improved arrhythmia recognition in ICD-systems.

P652 Left ventricular ejection fraction in magnetic resonance imaging as compared with Tc99 GSPECT

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Purpose: Impaired left vetricular (LV) function with decreased ejection fraction (EF) represents a frequent finding in patients with ischaemic heart disease. The present study aimed to assess the concordance of ejection fraction measured by MRI and scintigraphy,
Material: 30 patients (11 women, 19 men, mean age 57 SD 8 years) underwent MRI and Tc99 GSPECT during 3 consecutive days under the same treatment regimen. Patients were examined with a 1.5 T Magnetom Vision MRI-Scanner (Siemens, Erlangen, Germany). Global and segmental cardiac function were established with cine-Gradient Echo sequences (2-chamber transversal slice perpendicular to long axis of LV, slice thickness 8 mm) using ARGUS software. Cardiac cavity and myocardium were delineated manually in every single slice and phase of the cardiac cycle.
Ejection fraction in scintigraphy was assessed by gated-SPECT. Perfusion images were synchronized to electrocardiograms allowing for the measurement of segmental and global LV function.
Results: Mean LV EF measured by MRI was 46% SD 12%, mean LV EF measured by gated-SPECT was 44% SD 14%. NS, correlation r = 0.87,

Short axis two-chamber view.

Conclusion: Ejection fraction by MRI is highly concordant with gated SPECT, MRI is a non-invasive technique obviating the need of isotope injection.

P653 A generic approach for the integration of DICOM worklist management in cardiology

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Introduction Today, almost all modern image acquisition devices in medicine are equipped with a DICOM interface allowing for the exchange of DICOM images via network. In addition to the image data each DICOM object contains patient related and administrative data (i. e. patient's name and birth date, identifiers, examination date and time). Especially identifiers and patient data are needed to integrate the images in a picture archiving and communication system (PACS) and/or information system. The conventional way to store this kind of data in DICOM images is to re-enter it manually to the console of the acquisition device. However, this approach cannot ensure that the data is consistent with the information system. Furthermore, it takes time to enter the required information several times in different systems. To avoid these problems DICOM offers a dedicated service, called Modality Worklist Management. This service allows a modality to query a list of scheduled procedures from an information system. In cardiology DICOM Worklist Management is now supported by all major manufactures of catheterisation laboratories and ultrasound devices.
Material and methods: In our project we were faced to both different medical devices and different data models in the information systems. Therefore, apart from the implementation of the DICOM Worklist Management we had to solve the following issues:
– Translation of DICOM queries to SQL queries
– Freely configurable mapping of DICOM attributes and database elements
– General purpose database interface to support different database systems
Based on a freely available DICOM toolkit we developed a Worklist Management server that allows to query "work lists" from a database via SQL statements. A typical DICOM query consists of only a few matching attributes (e.g. date and time range). Our implementation first translates this query to a corresponding SQL statement which returns a set of procedure identifiers. In a second step, for each of these procedures the requested attributes are selected from the database, composed to a DICOM Worklist and sent back to the querying modality.
Conclusion The use of DICOM Worklist Management as a standardised network protocol in co-operation with an SQL database showed the following benefits:
– It is no longer required to enter data multiple times.
– Data inconsistencies are eliminated.
– A single program allows to communicate with different databases and modalities. Attaching a new system to the network only requires to adjust the configuration files.

P654 Changes of baroreflex latency during parasympathetic stimulation or inhibition support DeBoer model of cardiovascular system

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Purpose: There is growing evidence that prolonged phase shift (PS) between systolic blood pressure and heart rate oscillations may contribute to an unstable regulation of heart rate in patients with cardiac disease. Experimental studies have shown that inhibition of vagal activity caused the prolongation of PS and vice versa. DeBoer computer model of cardiovascular system (DBM) is based on beat-to-beat simulation of fast vagal and slow sympathetic action. It has already been shown that some features of the model are in agreement with the results of experimental studies. The aim of our study was to investigate whether changes of PS observed during experimental parasympathetic inhibition or stimulation could be explained by DBM.
Methods: 5-min records of systolic blood pressure and heart rate were generated by DBM for basal, decreased and increased vagal activity (100 simulations for each model setting). PS in low frequency band was assessed by cross-spectral analysis.
Results: PS under the baseline vagal tone (-55,7° ± 2,7°) was prolonged to -86,8° ± 0,4° or shortened to -35,0° ± 4,7° by the 50% reduction or 50% increase of vagal tone, respectively.
Conclusion: Results of the simulation are fully compatible with the findings of experimental studies and broadly support the validity of DBM. Although low frequency (baroreflex-related) oscillations represent resonance phenomenon due to the sympathetic and parasympathetic interactions, corresponding changes in baroreflex delay may be explained by the changes of parasympathetic modulation alone.

P655 Artificial neural networks versus bayesian classifiers for risk stratification following uncomplicated myocardial infarction

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Background and Aim: Artificial Neural Networks (ANN) are distributed networks of computing elements capable of identifying relations in input data that are not apparent with common analytic techniques. Although ANN have been applied to different problems in the diagnosis and treatment of coronary artery disease, definite data on prognostic value are lacking. This study was aimed to compare ANN and Bayesian classifiers in predicting outcome following myocardial infarction (MI).
Methods: 18 different clinical, exercise ECG and stress echo variables by 496 patients with uncomplicated MI were retrospectively analyzed to predict the cumulative end-point of cardiac death, nonfatal MI and unstable angina. Patients undergoing revascularization were censored. Short- (200 days), medium- (400 days) and long-term (1000 days) observation intervals, including 50%, 75% and 90% of the events and 477, 367 and 300 patients, respectively, were considered. At each interval any patient was binary assigned to the "event" or "no event" class. A Multi-layer Feedforward Network with 5-40 neurons/layer was built-up and trained using a Back Propagation algorhythm including variable learning rate and momentum term. The hold-out technique was used to separate training from validation set. Robust Bayesian classifier (RoC) using the leave-one-out technique was also derived. The accuracy of both analytic techniques in predicting outcome for each observation interval was compared to that obtained by assigning all subjects to the largest class (default accuracy, DA).
Results: 14 death, 27 nonfatal MI and 29 unstable angina occurred during 660± 549 days follow-up. The accuracy of ANN and RoC in predicting outcome are reported in the table.

	ANN			RoC		
	DA (%)	Acc (%)	Acc/DA	DA (%)	Acc (%)	Acc/DA
200 days	79	74	0.93	78	81	1.03
400 days	57	67	1.17	56	73	1.30
1000 days	61	64	1.04	62	68	1.10

Conclusions: 1) ANN do not improve the prognostic classification of patients with uncomplicated MI as compared to Bayesian Classifiers. 2) In particular, short-term prognostic accuracy seems insufficient.

P656 Dynamic SPECT with ^{123}I-BMIPP in patients with congestive heart failure: effect of angiotensin II type-1 receptor blockade

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Enhanced washout of iodine-123 beta-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) from 30 min to 4 hr images has been reported in patients with congestive heart failure (CHF). To investigate BMIPP kinetics in the early phase soon after tracer injection in patients with CHF, we performed dynamic single photon emission computed tomography (SPECT). We also examined effects of angiotensin II type-1 (AT1) receptor blockade on BMIPP washout in CHF patients. Twenty-nine patients with CHF and ten control subjects were examined. The consecutive 15 images of 2-min dynamic SPECT were acquired for 30 min after tracer injection. Echocardiography was carried out in all patients to evaluate left ventricular end-diastolic dimension and left ventricular ejection fraction. In the early phase after injection (0 to 4 min), a significant amount of radioactivity exists in the blood pool. After 6 min, myocardial BMIPP images were clear, and washout rate of BMIPP from 6 to 30 min was calculated. Washout rate (6 - 30 min) of BMIPP from the myocardium was faster in CHF than in control (8 ± 4% vs. -5 ± 3%, $P < 0.01$). Washout rate (6 - 30 min) of BMIPP from the myocardium demonstrated positive correlation with left ventricular dimension ($R = 0.54$, $P < 0.02$) and inverse correlation with left ventricular ejection fraction ($R = 0.53$, $P < 0.02$). Patients were given an AT1 receptor antagonist, candesartan, for 3 to 6 months, and dynamic SPECT was repeated. Enhanced washout rate of BMIPP from the myocardium in CHF was reduced after the treatment with candesartan (to -1 ± 4%, $P < 0.05$). These data suggest that 1) enhanced washout of BMIPP from the myocardium was observed soon after tracer injection in CHF patients, 2) the activation of angiotensin II signaling pathway is involved as an intracellular mechanism for enhanced BMIPP washout, and 3) improvement in fatty acid metabolism may represent a new mechanism for beneficial effects of AT1 receptor blockade on cardiac function and survival in CHF patients.

P657 Non-invasive magnetic resonance coronary artery imaging with CLARISCAN. Results from an international phase II trial

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Background: The non invasive diagnosis of coronary artery disease (CAD) with magnetic resonance techniques is burdened by a relatively low singal- and contrast-to-noise ratio. CLARISCAN (CS) is a strictly intravascular contrast agent based on iron. Aim of the study was to assess the efficacy and safety of CS for use with MR for imaging of the coronary arteries.
Methods: Seventy-nine patients were recruited in 10 centers in Europe and the United States using either breath hold or navigator techniques as different approaches for the diagnosis of CAD. Seventy-six patients were evaluable for safety, 73 for efficacy. Forty-five patients of the efficacy population were imaged with breath holding techniques, the remaining 28 with navigators to suppress breathing motion artifacts. Up to three MR-scans were performed for each patient with cumulative doses of £ 1.25 to 5.0 mg Fe/kg body weight. All patients were followed for 72 hours and examined with CXA for clinical indications before or after the MRA. The presence of significant stenoses (≥50% diameter reduction) was determined and compared to CXA in a blinded fashion.
Results: 123 significant stenoses (left main coronary artery: 3; right coronary artery: 40, left circumflex coronary artery: 35, left anterior descending coronary artery: 39, posterior descending coronary artery: 6) were found by CXA. In the most promising dose group (> 2.5-3.75 mg Fe/kg b.w.) diagnostic accuracy of MRA was 81.3% for the right and left main coronary artery. No serious adverse events were observed.
Conclusions: The use of CS for noninvasive MR coronary artery imaging is safe, the most promising dose group was >2.5-3.75 mg Fe/kg b.w. Diagnostic accuracy was improved in comparison to recent literature.

P658 Cardiac phosphorus-31 magnetic resonance spectroscopic imaging (^{31}P-MRSI) in patients with hereditary haemochromatosis

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Purpose: Hereditary hemochromatosis (HHC) causes increased iron storage and is often associated with liver cirrhosis, liver cancer, and restrictive cardiomyopathy. The purpose of this study was to detect alterations of cardiac high-energy phosphate metabolism in patients with hereditary hemochromatosis prior to the development of structural heart diseases. Therefore cardiac phosphorus-31 magnetic resonance spectroscopic imaging (31P MRSI) was employed.
Methods: 24 male patients (mean age 47.2 ± 12 a) with homozygous hemochromatosis and 24 male healthy volunteers (mean age 47 ± 11 a) as age matched controls were included in this study. Transthoracal echocardiography was employed to all subjects in order to exclude structural heart diseases. Using a 1.5 Tesla whole-body MR scanner ECG-triggered transversal 31P MRSI was performed. For each subject a mean PCr/β-ATP value of the left ventricle was determined.
Results: No significant differences in blood lipid levels between hemochromatosis patients and healthy volunteers were observed. Left ventricle mean PCr to β-ATP ratio of patients with hereditary hemocromatosis (1.64 ± 0.35) was significantly decreased ($p<0.001$) in comparison to healhy volunteers (2.26 ± 0.52). Additionally, we detected a moderate correlation between PCr to β-ATP ratios and ejection fractions ($r=0.54$; $p=0.003$)
Conclusion: This study shows that 31P MRSI permits the detection of alterations of cardiac high-energy phosphate metabolism in patients with hereditary hemochromatosis prior to the development of structural heart diseases. The decreased PCr to β-ATP ratios in HHC might be caused by mitochondrial impairment due to cardiac iron overload.

P659 High-dose dobutamine stress MRI for follow-up after coronary revascularization procedures in patients with wall motion abnormalities at rest

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Introduction: We determined the value of high-dose dobutamine stress MRI (DSMR) for diagnosis of ischemia in patients (pts) with known coronary artery disease (CAD), prior coronary revascularization procedures, and wall motion abnormalities at rest.
Methods: 160 consecutive pts (59±8 years; prior myocardial infarction: 63%; prior percutaneous or surgical revascularization in 90% and 28%, respectively) underwent DSMR (1.5 T Philips) prior to clinically indicated invasive coronary angiography. Images were acquired at rest and during a standardized high-dose dobutamine-atropine protocol in 3 short-axis, a 4- and a 2-chamber view, using a single-slice segmented turbo gradient echo technique (TR/TE/flip 5.6/1.9/25; spatial resolution ≤ 1.5x2.5x8 mm; temporal resolution<30 ms). Regional wall motion was assessed by consensus between 2 blinded observers using a multiple screen format (MASS 4.2, Medis), a 16 segment model and a four-point scoring system. A new or worsening wall motion abnormality in ≥1 segment was considered positive for ischemia.
Results: 195 significant coronary artery stenoses (≥50% diameter by QCA) were found in 119 pts (74%). High-dose DSMR was successfully performed with diagnostic image quality in all pts. However, target heart rate was not reached in 9 pts (6%), due to end of protocol in negative submaximal examinations in 4 pts (3%), and limiting side effects in 5 pts (3%), including ventricular extrasystoly (n=2), severe chest pain (n=1), nausea (n=1) and asymptomatic decrease in blood pressure (n=1). Other major side effects included a case (0.6%) of sustained ventricular tachycardia (VT) with hemodynamic compromise requiring external defibrillation, 2 cases (1.3%) of non-sustained VT, as well as one case (0.6%) of atrial fibrillation with rapid ventricular rate. Overall sensitivity and specificity of DSMR for diagnosis of significant CAD were 89% and 85%, respectively. Diagnostic accuracy was 88%, positive and negative predictive value 94% and 73%, respectively. Sub-group analyses for pts with prior myocardial infarction or coronary artery bypass grafting yielded similar results. Overall sensitivity for detecting significant CAD in pts with one (n=64), two (n=34) or three (n=21) diseased vessels was 87%, 91% and 100%, respectively.
Conclusions: High-dose DSMR is reasonably safe and feasible in pts with known CAD, and can be used for follow-up after coronary revascularization procedures. Diagnostic accuracy is similar to MR data reported for pts with suspected CAD, and compares favorably with other established noninvasive techniques.

P660 Coronary flow reserve: a clue to the explanation of Tl-201 redistribution patterns early after reperfusion therapy for myocardial infarction

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Tl-201 reverse redistribution is commonly observed on stress-redistribution Tl-201 scintigrams (SPECT) after successful reperfusion therapy for acute myocardial infarction (AMI). The pathophysiology of such phenomenon remains unclear.

Methods: We studied 41 consecutive patients with successful primary stenting for a first AMI and single vessel disease. All patients underwent dipyridamole stress-redistribution SPECT 6-10 days after the AMI followed within 24 hours by coronary and left ventricular angiography, and intracoronary doppler assessment of coronary flow reserve (CFR). SPECT, Coronary and left ventricular angiography were repeated at 6 month follow-up.

Results: In-hospital SPECT showed fixed defect in 8, stress defects with significant rest redistribution in 7, reverse redistribution in 21 and absence of defect in 5 patients. On follow-up SPECT only 5 patients showed reverse redistribution. The comparison of patients with rest redistribution and those with reverse redistribution is reported in the table.

Rest versus reverse redistribution

	Rest redistribution (n=7)	Reverse redistribution (n=21)	p
In-hospital stress defect (%)	22±22	12±14	NS
In-hospital rest defect (%)	17±19	18±16	NS
LV end systolic volume (ml/m^2)	36±9	25±11	0.02
Coronary flow reserve	2.8±0.9	2.2±0.5	0.03
Follow-up rest defect (%)	11±15	10±16	NS
Segments with contractility recovery (n)	1.3±1.7	3.1±2.1	0.04

LV: left ventricular

Conclusions: Compared to the redistribution pattern, reverse redistribution is associated with lower CFR but less remodelling and better contractility recovery despite similar infarct size. These findings are suggestive of a deeper myocardial functional injury in the redistribution pattern and a reversible decrease of vasodilator reserve in the infarct-related artery in the reverse redistribution pattern.

P661 Real-time two-dimensional cardiac strain imaging utilizing cardiac echo-elastography for the quantitative evaluation of coronary artery disease

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We developed real-time cardiac elastography as a novel method for obtaining two-dimensional (2-D) strain (the degree of deformity) by imaging myocardial displacement and displaying strain in a 2-D parametric image. Doppler tissue derived strain imaging is one-dimensional, angle dependent and limited by cardiac translation. We thus utilized two-dimensional gray scale (2-D) radiofrequency (RF) data to derive strain images.

Methods: 5 subjects (2 CAD pts, 3 normals) were examined with a GE Vivid FiVe echo unit. RF data were displayed as 2-D elastogram cine-loops. Elastograms are obtained by comparing subsequent RF frames, using cross-correlation to detect tissue displacements, whose gradient is strain. The imaging frame rate was 50 frames/second, which enables tracking of small compressions (1%) of the heart muscle and limits motion artifacts. Strain can then be displayed in parametric images with uni or two-directional color scales. Two observers performed qualitative visual assessments (QVA) of the strain distribution. Spatial and dynamic 2-D and spatial A-mode interrogation allowed for the quantitative assessment of regional and dynamic strain throughout the cardiac cycle. In the parasternal long axis view % peak strain of the anteroseptal (AS), posterior wall (PW) and papillary muscle (PM) was measured.

Results: Inhomogeneous spatial and temporal strain distribution was observed both in normal subjects and in patients. Peak strain was greatest in patients at the level of the papillary muscle at both endsystole and enddiastole and strain distribution was heterogene. Normal subjects showed a more uniform distribution of spatial strain within the heart and of temporal strain throughout the cardiac cycle.

Conclusions: 1) Differences in the heterogenicity of spatial and temporal strain can be observed in real time and two-dimensionally between normal subjects and patients with coronary artery disease using this novel method, which we call 'echo-elastography'.

2) 2-D, real-time derived cardiac echo-elastography provides qualitative and quantitative strain imaging without translation artifacts, and may be feasible for a novel comprehensive evaluation of regional left ventricular function in coronary artery disease.

GENETIC AND DIAGNOSTIC ASPECTS IN HYPERTROPHYC CARDIOMYOPATHY

P662 Hypertrophic cardiomyopathy: clinical expression of Arg278Cys missense mutation in the cardiac troponin T gene

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Introduction: The clinical characteristics of patients with hypertrophic cardiomyopathy (HCM) differ depending on the particular genetic mutation. Mutations in the cardiac troponin T (cTnT) gene are considered associated with reduced penetrance, onset on adolescence, mild cardiac hypertrophy and a high incidence of sudden death at a young age.

Methods: We studied, clinically and genetically, 143 consecutive unrelated patients with HCM. Family members whose probands had an Arg278Cys mutation were also studied. All underwent physical examination, ECG and echocardiography. Clinical records and family histories were obtained. DNA was extracted from peripheral blood and the hot-spot exons 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 15 and 16 of the cTnT gene were amplified by polymerase chain reaction (PCR). Automatic sequencing identified the presence of misalignments and a new PCR was performed for each suspicious case. Results were verified by resequencing 3 times in forward and reverse order as well as with single strand confirmation polymorphism (SSCP). Family members and 100 normal individuals were screened by automatic sequencing, SSCP and restriction enzyme analysis for areas of interest.

Results: An Arg278Cys missense mutation was identified in two probands. In the first family, the mutation was identified in one other living member with HCM. The disease in this family is characterized by late onset (mean age 43.3±9.8 years), mild cardiac hypertrophy (mean wall thickness of 17±3 mm) and a high incidence of sudden death at older ages (six cases of sudden death at a mean age of 66±3.6 years). Based on clinical data, the second proband seems to carry a de novo mutation. He was a boy with asymmetric septal hypertrophy (maximum wall thickness of 22 mm) who died suddenly at the age of 15 years. Neither parent fulfilled the diagnostic criteria reported for HCM in 1st degree relatives of patients and the family history was free from cardiac disease and sudden deaths.

Conclusions: Our data suggest that the Arg278Cys mutation in the cTnT gene can present with a clinical profile which deviates from what is currently expected for the cTnT gene mutations. Furthermore, the same mutation can have a different clinical expression in different families.

P663 Mybpc3 not myh7 is the predominant gene mutated in a large cohort of unrelated consecutive patients with hypertrophic cardiomyopathy

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Defects in ten sarcomeric genes are known to cause hypertrophic cardiomyopathy (HCM). Mutation types and frequencies in large cohorts of consecutive and unrelated patients have not yet been determined. We therefore screened 108 unrelated and consecutive HCM patients for mutations in six sarcomeric genes: cardiac myosin-binding protein C (MYBPC3), β-MHC (MYH7), Troponin T (TNNT2), a-Tropomyosin (TPM1), Troponin I (TNNI3), and Troponin C (TNNC1).

HCM was diagnosed by echocardiography (septum > 15 mm, septal/posterior wall >1.3), angiography or based on a state after myectomy. Single-strand conformational polymorphism (SSCP) analysis was used for mutation screening, followed by sequencing. Sensitivity was determined in comparison with denaturing high-performance liquid chromatography (DHPLC) and reached > 97%. A total of 34 mutations in 36 out of 108 patients were identified: 18 mutations in MYBPC3 in 20 patients, two of them being founder mutations; 13 missense mutations in MYH7 in 14 patients, one of them being a founder mutation (R870H); one amino acid exchange in TPM1, TNNT2 and TNNI3, respectively. No disease-causing mutation was found in TNNC1. Twenty-eight of the 36 mutation carriers (78%) reported a positive family history with at least one affected first-grade relative, only 8 mutations occurred sporadically (22%).

MYBPC3 was the gene that most frequently caused HCM in our cohort of unrelated patients. Systematic mutation screening in large samples of HCM patients leads to a genetic diagnosis in about 30% of unrelated index patients and in about 57% of patients with a positive family history.

P664 ^{123}I-MIBG scintigraphic assessment of sympathetic innervation in hypertrophic cardiomyopathy patients with and without severe tachyarrhythmias

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Aim: We sought to evaluate scintigraphic myocardial sympathetic innervation in hypertrophic cardiomyopathy (HCM) patients (pts) with and without lifethreatening ventricular.
Methods: We studied 40 HCM pts: n.10 with ventricular tachycardia or fibrillation (Group A); n.10 with ventricular myocardial dysfunction (Group B); n.10 with other sudden death risk factors (Group C); n.10 with absence of any previous features (Group D), and ten healthy subjects (controls). Myocardial sympathetic innervation and perfusion were assessed by Iodine-123-metoidobenzylguanidine(I-123-MIBG) and N-13 ammonia (NH3) scintigraphic imaging, respectively. Heart/lung ratio for I-123-MIBG uptake (H/L) and a score index (higher values=lower uptake) of NH3 uptake (SI-NH3) as well as of myocardial areas having normal NH3 with reduced I-123-MIBG uptake (SI-MIBG) were provided.
Results: Reduced H/L ratio and higher SI-MIBG were found in the HCM pts compared to the controls (H/L=1.29±0.1 vs 1.61±0.1, p<0.0001; SI-MIBG=8.5±2.9 vs 2.2±2.2, p<0.0001).Group A HCM pts with ventricular tachycardia/fibrillation, when compared with groups B+C+D pts, had lower SI-MIBG uptake (2.5±1.7 vs 10.3±3, p=0.0001), younger mean age (33yrs±16 vs 49yrs±12, p=0.004), and increased maximal left ventricular wall thickness (25mm±4 vs 20mm±4, p=0.04). Higher SI-MIBG characterized group B HCM pts with ventricular myocardial dysfunction (16.2±3.6 vs 5.9±2.7of groups A+C+D, p< 0.0001).
Conclusions: In HCM, normal sympathetic innervation is detectable in patients with severe ventricular tachyarrhythmias, while remarkable denervation is correlated with ventricular myocardial dysfunction. These findings may entail potential impact on diagnostic and therapeutic approach of HCM pts.

P665 Evidence for the detection of intramural fibrosis in hypertrophic cardiomyopathies by contrast-enhanced MRI

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Background: Fibrotic areas in patients with hypertrophic cardiomyopathies (HCM) were described in different histological studies. Applying contrast enhanced Magnetic Resonance Imaging (MRI) it is possible to characterise myocardial infarctions. The visualisation is based on the phenomenon of the decelerated contrast wash-in/washout leading to "delayed enhancement" (DE).
Patients and methods: We investigated 21 patients with different forms of HCM (non obstructive, NHCM: n=10; obstructive; HOCM, n=11) in a 1,5T MR system (Signa CV/i, GE Medical Systems). Applying an inversion-recovery prepared T1-weighted gradient echo sequence, DE patterns were assessed after intravenous application of a bolus of GD-DTPA (0.2 mmol/kg BW).
Results: The patient groups (HOCM; NHCM) show significant differences in the mass (NHCM 199±14 vs HOCM 278±32, p< 0,01), no differences in the age, maximal septal wall thickness (MSWT) and in the left ventricular ejection fraction. (EF). In 64%of the patients with HOCM and in 50% of the patients with NHCM a local DE was detectable. The contrast enhancement was mostly found in the septal wall. No correlation was found between the presence of DE to mass, EF, or MSWT. DE distribution was focal, neither subendocardial nor transmural.

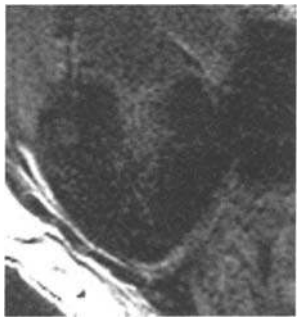

Fig. 1: Focal septal contrast enhancement.

Discussion: Contrast-enhanced MRI shows areas of increased contrast uptake in HCM not related to the extent of hypertrophy or the functional status. The localisation and extent also differs from that of classical myocardial infarction. Thus, the detected areas are likely to represent "myocardial disarray" or areas of fibrotic tissue transformation. The prognostic value of these findings has to be further elucidated.

P666 Right ventricular myocardial function in either physiological or pathological left ventricular hypertrophy: a tissue Doppler study

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Aim of the study: to analyze right ventricular (RV) myocardial function in patients with left ventricular (LV) hypertrophy secondary to either hypertrophic cardiomyopathy (HC) or athlete's competitive endurance training.
Methods: Standard Doppler echo and pulsed Tissue Doppler (TD) of posterior septal wall, mitral and tricuspid annulus were performed in 32 top-level endurance athletes (AT) and in 26 patients with HC, all men, both having evidence of LV hypertrophy. The following parameters of both RV and LV myocardial function were assessed: systolic peak velocities (Sm), pre-contraction time (PCTm), contraction time (CTm), early (Em) and late (Am) diastolic velocities, Em/Am, relaxation time (RTm).
Results: the two groups were comparable for age and blood pressure, while AT showed lower heart rate (HR) and increased body surface area than HC. LV mass index was not significantly different between the two groups. However, septal thickness was higher in HC, while both LV and RV end-diastolic diameters and LV stroke volume were increased in AT. All transmitral and transtricuspid Doppler indexes were higher in AT, with increased E/A ratios. TD analysis showed in HC lower Sm, Em and Em/Am ratio as well as longer RTm and PCTm at the level of all the analyzed segments. These differences remained significant even after correction for age, HR and LV mass index. By univariate analysis, peak Em of tricuspid anulus was positively related to LV end-diastolic diameter in AT ($r = 0.76$, $p < 0.0001$) and inversely associated to septal thickness in HC ($r = -0.69$, $p < 0.001$). After adjusting for HR, age and LV mass index, distinct multiple linear regression models confirmed the independent positive association between RV peak Em velocity and LV end-diastolic diameter (β coefficient = 0.75, $p < 0.0001$) in AT, and independent inverse correlation of the same peak Em velocity of tricuspid annulus with septal thickness ($\beta = -0.62$, $p < 0.001$) in HC. Of interest, a RV Em peak velocity < 0.16 m/sec differentiated AT and HC better than standard Doppler (92% sensitivity and a 93% specificity).
Conclusions: Early diastolic right ventricular myocardial function is positively influenced by preload increase in AT and negatively associated to increased septal thickness in HC. Therefore TD may represent a useful tool in the differential diagnosis between athlete's heart and HC, underlining the different involvement of RV myocardial function in either physiological or pathological LV hypertrophy.

P667 The incidence of cardiac variant Fabry disease in patients with hypertrophic non obstructive cardiomyopathy (HNCM)

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Introduction: Regarding the cardiac variant of Fabry disease (FD) there are several case reports in the literature; cardiac hypertrophy as the only manifestation of the disease mimicks the clinical features of HNCM. Based on recently reported therapeutic progress,major attention has been paid to FD. However, systematic investigations concerning the frequency of cardiac variant FD in HNCM are still lacking. Diagnostic pitfalls may arise from the fact that invasive diagnostic procedures are not provided in the diagnosis of HNCM. Especially concealed myocardial storage disease has to be excluded to avoid potential pitfalls in genetic studies and to avoid wrong therapeutic consequences.
Methods: Therefore, we performed right ventricular endomyocardial catheter biopsy (EMCB) for the first time in a systematic investigation in a large group of pts. (287 consecutive pts. and 13 non consecutive pts.)with HNCM (mean age 55 years;range 14 to 90 years).
Results: In unexpected many pts.(26 from 300 pts.; 8,7%) EMCB turned out concealed cardiac FD. This was only possible by electron microscopic evaluation of EMCB. In 12 of these pts. (4,0%) the diagnosis of FD was stated on the basis of electron microscopic evaluation.In 14 pts. (4,7%) the morphological alterations were not as pronounced as in the first group; therefore only the strong suspicion of FD was stated in these pts.. However,in 2 of these pts. alpha-galactosidase A was evaluated resulting in a pathological low residual enzyme activity in plasma. Evaluation by electron microscopy revealed in all pts. concentric lamellated structures with parallel orientation typical of FD.
Conclusion: The incidence of concealed cardiac FD in pts. with HNCM (26 of 300 pts.; 8,7%) is unexpected high. However these findings fit favourably with those of Nakao (cardiac variant FD in 7,5% of pts. with clinical suspicion of hypertrophic cardiomyopathy) and coworkers (Nakao et al.New Engl J Med 1995;333:288-293). Therefore invasive diagnostic procedures including EMCB are mandatory in all pts. with HNCM and concealed myocardial storage disease,especially cardiac FD has to be ruled out. This is of importance to avoid potential pitfalls in performing genetic studies. Additionally, based on recently reported therapeutic progress in enzyme replacement therapy of FD, this is of special clinical importance thus offering a potential causal therapeutic option in pts. with clinical features of HNCM.

P668 Serum markers of interstitial myocardial collagen in hypertrophic cardiomyopathy

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Background: Increased interstitial collagen is a characteristic of hypertrophic cardiomyopathy (HCM) and is a determinant of increased myocardial stiffness. Our study aims at assessing if collagen turnover is altered in HCM.
Methods: We studied 35 HCM patients (27 men; mean age 35±9 years) and 13 age- and sex-matched healthy volunteers (9 men; mean age 35±11 years). Collagen turnover was assessed by measuring, by radioimmunoassay, serum concentrations of 3 by-products of collagen metabolism: procollagen III N-terminal propeptide (PIIINP), an index of collagen III synthesis; procollagen I C-terminal propeptide (PICP) and C-terminal telopeptide of collagen I (ICTP), indexes of collagen I synthesis and degradation, respectively. Besides, we measured by ELISA serum levels of matrix metallo-proteinase 1 (MMP-1), a collagenase: MMP-1 activity, free MMP-1 (i.e. the active form and its precursor), total MMP-1 (i.e. free MMP-1 and MMP-1 blocked by the tissue inhibitor of metalloproteinase-1 (TIMP-1)). In addition, we measured TIMP-1.
Results: Serum concentration of PIIINP, ICTP and TIMP-1 were higher in HCM than in controls (Table). As expected, total MMP-1 values were below the method's resolution for controls, as well as for HCM.

	Controls	HCM	p
PIIINP	2.45 ± 0.63	3.34 ± 1.29	0.003
PICP	184 ± 61	186 ± 68	N.S.
ICTP	2.37 ± 0.39	2.83 ± 0.74	0.046
MMP-1 activity	7.66 ± 4.56	8.38 ± 4.84	N.S.
Free MMP-1	9.80 ± 5.22	11.04 ± 6.35	N.S.
Total MMP-1	6.02 ± 0.65	5.98 ± 0.32	N.S.
TIMP-1	890 ± 177	1021 ± 167	0.045

Conclusions: In HCM patients, collagen III tends to build up, while collagen I is degraded. Degradation is altogether hampered as TIMP-1 is increased.

P669 Increased circulating levels of procollagen peptides in patients with hypertrophic cardiomyopathy

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Background: Myocardial fibrosis is found in the ventricular wall and associated with myocardial dysfunction in patients with hypertrophic cardiomyopathy (HCM). Recent studies suggested that circulating levels of procollagen peptides are associated with myocardial fibrosis in heart disease. Therefore, this study was designed to elucidate whether the circulating levels of procollagen peptides are elevated in patients with HCM, especially to evaluate the effects of angiotensin II receptor blocker (ARB) on collagen synthesis in patients with HCM who had the occurrence of congestive heart failure (CHF).
Methods: Eighty-six patients with HCM and 10 normal control subjects participated in this study. The HCM patients were divided into 2 groups; 74 with HCM and 12 with HCM who had the history of CHF (HF-HCM). Serum levels of carboxy-terminal propeptide of procollagen type I (PIP) and procollagen type III amino terminal peptide (PIIIP) were measured. Left ventricular systolic function was examined using fractional shortening (FS) by echocardiographically examination. We also determined the effects of ARB on collagen synthesis in 6 patients of 12 patients with HF-HCM who had been treated with ARB.
Results: 1) Serum levels of PIP and PIIIP were significantly higher in patients with HF-HCM than those in patients with HCM and normal control subjects ($p < 0.0001$, $p < 0.05$, respectively). 2) There was a significant correlation between serum levels of PIP and FS in all HCM patients ($r = 0.471$, $p = 0.0012$). 3) PIP and PIIIP decreased in all 6 HF-HCM patients after the treatment with ARB ($p < 0.001$).
Conclusion: Our findings indicate that circulating levels of procollagen peptides may be related to the disease progression of HCM and that ARB has the potential to attenuate collagen synthesis and myocardial fibrosis in patients with HCM.

P670 Brain natriuretic peptide in hypertrophic cardiomyopathy with and without systolic dysfunction

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Background: Increased plasmatic levels of Brain Natriuretic Peptide (BNP) have been observed in both dilated (DCM) and hypertrophic cardiomyopathy (HCM). We determined whether BNP can be a biologic marker of HCM progressing to systolic dysfunction.
Methods: Patient population consisted of 10 HCM patients (pts) with normal systolic function (ejection fraction (EF) >60%) (Group 1) and 10 HCM pts with depressed contractility (EF<50%) (Group 2). The diagnosis of HCM was supported by 2D-echocardiography, cardiac catheterisation, coronary angiography and left ventricular (LV) endomyocardial biopsy. LV mass was calculated according to Devereux formula. BNP plasma concentrations were measured using specific immunoradiometric assay on plasma samples obtained from the femoral vein during cardiac catheterisation after at least 72 hours withdrawal of cardiovascular drugs. In 4 pts with systolic dysfunction, BNP levels were retrospectively assessed in plasma samples collected and stored at -80°C at the time of diagnosis when pts were on normal contractile function. As controls we used 10 healthy pts. Unpaired t-test was used to compare BNP levels and echocardiographic measurements.
Results: All patients were in sinus rhythm. No patient showed an intraventricular gradient. Mean LV end-diastolic diameter was 44.0±3.4 mm in Group 1 and 54.0±4.69 mm in Group 2. Mean EF was 63.4±3.82% vs 41.7±6.5%. BNP levels in HCM pts were higher than in controls and in Group 2 were significantly higher than in Group 1 (343.5±27.0 pg/ml vs 68.7±22 pg/ml) ($p<0.001$). In particular BNP levels in pts with HCM and systolic dysfunction were >4 times higher than in HCM with normal contractility. There were no statistically significant differences in left ventricular mass, left atrial dimensions and end-diastolic pressure between the two groups. A further increase of BNP was observed in the four pts who had BNP assessed during normal and depressed systolic function (316.2±21.0 pg/ml vs 88.9±24 pg/ml) ($p<0.001$).
Conclusions: In HCM plasma BNP is significantly higher in pts with systolic dysfunction than in pts with normal contractility. BNP can be used in HCM as a biologic marker of disease progression.

P671 Hypertrophic cardiomyopathy: significance of raised BNP levels

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The significance of raised plasma BNP in hypertrophic cardiomyopathy (HCM) remains unclear and there is some controversy about the relationship between BNP levels and left ventricular diastolic dysfunction.
Methods: we studied 37 members of HCM families. Nineteen (group A) – mean age 51.5 ± 15.8 years, 11 women – were affected; 18 (group B) – 27.3 ± 12.7 years, 14 women – had no phenotypic expression of the disease. In group A, 3 pts. had sub aortic obstruction (OB), one of them also had moderate mitral regurgitation (MR). All the individuals had a non-dilated well contracting left ventricle (Ej.Fr.> 55%). Plasma concentrations of BNP were measured using specific electrochemiluminescence immunoassay for proBNP (Elecsys), values being expressed in pg/ml. A score of left ventricular hypertrophy (LVHS) was derived from the sum of the thicknesses of 9 segments (8 short axis view segments – 4 subvalvular, 4 at papillary muscles –and 1 apical view – apex). Four parameters that can be related to left ventricular diastolic function - left atrial dimension (LAD), left atrial fractional shortening (LAFS), difference in duration between reverse pulmonary wave (R) and mitral A wave and isovolumetric relaxation time (IVRT) - were calculated by ECHO. Values of BNP and ECHO parameters obtained in groups A and B were compared. In group A, BNP values were compared with ECHO findings.
Results: BNP levels did not correlate with age in both groups. Group A had abnormal BNP values and ECHO indices and differed significantly from group B (see table).

Comparison between group A and B

*BNP (pg/ml)	A - 951.4±1596.8	versus	B - 44.6±41.3	p<0.05
LVHS (mm)	A - 15.6±3.9	versus	B - 8.9±1.1	p<0.001
LAD (mm)	A - 44.0±8.1	versus	B - 34.0±4.2	p<0.001
LAFS (%)	A - 29.0±9.7	versus	B - 43.0±16.3	p<0.005
IVRT (ms)	A - 97.4±36.82	versus	B - 78.0±11.6	p<0.05

* (BNP value patient with OB - gradient 110 mmHg - and MR was 7147 pg/ml)

In group A, there was a positive correlation between BNP plasma levels and LVHS ($r = 0.63$; $p < 0.005$) but no correlation was found with the other ECHO parameters.
Conclusions: In hypertrophic cardiomyopathy, raised plasma BNP reflects the presence and severity of left ventricular hypertrophy rather than left ventricular diastolic dysfunction.

P672 Impaired passive diastolic function correlates to increased collagen synthesis and blunted degradation in hypertrophic cardiomyopathy

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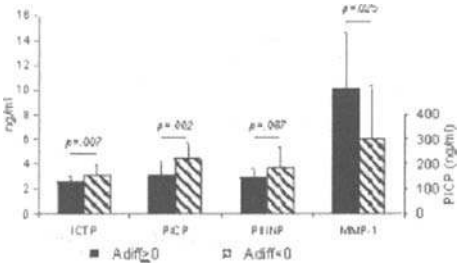
Background: Hypertrophic cardiomyopathy (HCM) is characterized by LV hypertrophy and increased interstitial fibrosis, which may contribute to diastolic dysfunction. We previously showed that patients with noninvasive signs of LV diastolic dysfunction had higher serum levels of PIIINP, a product of collagen III synthesis, and ICTP, a product of collagen I degradation.
Methods: We studied 36 HCM patients, 27 men, mean age 35±6 years. By echocardiography, we assessed diastolic function as: the pattern of LV filling (normal or impaired relaxation vs pseudonormal or restrictive), and the difference in duration between antegrade A wave and retrograde pulmonary vein flow (Adiff, ms): it indicates increased LV end-diastolic pressure if <0. Collagen turnover was assessed by measuring serum concentrations of PICP, a product of collagen I synthesis, PIIINP, and ICTP (radioimmuno assay), and in 28 of 36 patients serum activity of MMP-1 (Matrix Metallo-Proteinase-1, ELISA), a collagenase.
Results: ICTP and PICP were inversely related to age (r=-.462, and r=-.541, respectively, p<.005). Patients with Adiff<0 had higher ICTP, PICP, and, albeit not significantly, PIIINP, and lower MMP-1 (Figure). Patients with pseudonormal or restrictive filling patterns had higher values of ICTP and PICP (3.1±.8 vs 2.5±.5 ng/ml, and 208±69 vs 163±60 ng/ml, respectively, p<0.05), and lower values of MMP-1 (6.2±4.1 vs 10.3±4.7 ng/ml, p=0.02) than patients with normal or impaired relaxation filling patterns.



Conclusions: HCM patients with impaired passive diastolic function (as assessed by Adiff<0 and pseudonormal or restrictive filling patterns) tend to build up collagen, resulting from both increased collagen synthesis and blunted degradation.

RESUSCITATION AND AUTONOMIC EXTERNAL DEFIBRILLATOR

714 Risk factors for out-of-hospital cardiac arrest in the community. The Reykjavik study.

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The purpose of our investigation was to study whether risk factors for out-of-hospital cardiac arrest could be determined among the baseline characteristics of the cohort of the Reykjavík Study, a prospective community based cohort study that started in 1967.
The correlation of potential risk factors and out-of-hospital cardiac arrest was investigated in this cohort of 8007 men and 9435 women,who were alive in 1987. From 1987 to 1996 181 individuals, i.e. 137 men and 44 women sustained out-of-hospital cardiac arrest due to cardiac causes. The cause for cardiac arrest was obtained from hospital medical records and the death certificates of those who died and had not been admitted to hospital.
The following variables were examined: age, height, weight, cholesterol, triglycerides, systolic and diastolic blood pressure,antihypertensives, smoking history, diabetes mellitus, family history of myocardial infarction, old MI, silent MI, angina pectoris, heart size on chest X-ray and erythrocyte sedimentantion rate. The electrocardiogram was examined for arrhythmias and various other abnormalities, classified by the Minnesota Code. The independent contribution of each of these variables was determined by Cox regression analysis. The summary of significant variables by multivariate analysis is presented in the table.
Conclusion: The risk of sustaining out-of-hospital cardiac arrest is significantly increased in men with higher age, increased BMI, high cholesterol, hypertension, smoking, and a history of MI. For women, the risk was increased by elevated levels of cholesterol and triglycerides, systolic blood pressure and increased voltage on ECG.

Summary of significant variables

	Men RR (95%CI)	P	Women RR (95%CI)	P
Age 1987	1.04(1.02-1.07)	0.0005		
BMI,kg/m^2	1.06 (1.02-1.11)	0.008	0.87 (0.80-0.95)	0.0013
Cholesterol mmol/L	1.45 (1.26-1.68)	0.0000	1.38 (1.12-1.70)	0.0026
Triglycerides mmol/L			2.18 (1.10-4.32)	0.0256
Hypertension	1.54 (1.09-2.19	0.0157		
Systolic blood pressure mmHg			1.01 (1.00-1.03)	0.0315
Current smoker	1.75 (1.14-2.46)	0.0014		
Sustained MI	3.87 (2.41-6.21	0.0000		
ECG (increased voltage)			14.4 (5.46-38.45)	0.0000

715 Tripling survival from sudden cardiac arrest via early defibrillation, without traditional education in cardiopulmonary resuscitation

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Background: Sudden cardiac arrest (SCA) claims an estimated 350,000 lives per year in the United States, representing a major public health problem. The vast majority of SCA is caused by ventricular fibrillation (85%) where early defibrillation is the most important intervention affecting survival. After 10 minutes, very few resuscitation attempts are successful (0-2%). The major determinants of survival after witnessed out-of-hospital SCA include bystander initiation of cardiopulmonary resuscitation (CPR) with early defibrillation and the rapidity with which defibrillation is accomplished. However, traditional CPR is difficult to teach, to be correctly performed and to retain the skill if not performed routinely. To improve public access to early defibrillation, we established "Piacenza Progetto Vita", (PPV) the first system of out-of-hospital early defibrillation by first responder volunteers, trained in use of the external biphasic defibrillators (AED), without traditional education in CPR
Methods: The system serves a population of 173,114 residents in the Piacenza region, Italy. Equipment for the system comprises 39 semi-automatic (AEDs): 12 placed in high-risk locations, 12 in lay-staffed ambulances and 15 in police-cars; 1285 lay volunteers were respond to all cases of suspected SCA, in co-ordination with the Emergency Medical System (EMS).
Results: During the first 22 months, 354 SCA occurred (72±12 years, 73% witnessed). The PPV volunteers treated 143 SCA cases (40.4%) with an EMS call to arrival time of 4.8±1.2 min (vs. 6.2±2.3 min for EMS, p=0.05). Overall survival rate to hospital discharge was tripled from 3.3% (7/211) for EMS intervention to 10.5% (15/143) for PPV intervention (p=0.006). The survival rate for witnessed SCA was tripled by PPV: 15.5% vs. 4.3% in the EMS treated group (p=0.002). A "shockable" rhythm was present in 23.8% (34/143) of the PPV patients vs. 15.6% (33/211) of the EMS patients (p=0.055). The survival rate from shockable dysrythmias was higher for PPV vs. EMS: 44.1% (15/34) vs. 21.2% (7/33), p=0.046. The neurologically intact survival rate was higher in PPV vs. EMS treated patients: 8.4% (12/143) vs. 2.4% (5/211), p=0.009.
Conclusion: Broad dissemination of AEDs for use by non-medical volunteers without traditional education in cardiac-pulmonary resuscitation, enabled early defibrillation and tripled the survival rate from out-of-hospital SCA.

716 Prediction of neurological outcome after cardiac arrest by serial determination of serum neuron-specific enolase – experience with 100 patients

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Neuron-specific enolase (NSE) is increasingly used as a marker of hypoxic brain damage. The purpose of this prospective study was to evaluate the prognostic value of NSE after cardiopulmonary resuscitation.

Methods: We examined 121 consecutive patients (pts) (80 men, 41 women, age 16 to 89 years, mean 66) who returned to spontaneous circulation after cardiac arrest (ventricular fibrillation in 68, asystole in 23, and pulseless electrical activity in 30) but were unconscious and mechanically ventilated. Serum NSE concentrations (Cobas Core NSE EIA, Roche, normal range 0-15 ng/ml) were determined at admission (day 0) and on the following 4 days. Hemolytic samples were discarded. Pts were classified according to the "best-ever achieved" Glasgow-Pittsburgh cerebral performance categories (CPC, 1 to 5) of the Utstein recommendations. Twenty-one of the 121 pts were excluded from the study because they died while under analgesia sedation, leaving 100 patients for analysis.

Results: 61 of the 100 included pts were discharged from intensive care after a median (range) of 6 (1-76) days with good cerebral performance (CPC 1 in 21 pts), moderate cerebral disability (CPC 2 in 25 pts) or severe cerebral disability (CPC 3 in 15 pts). The remaining 39 pts were discharged in a comatose state (CPC 4 in 28 pts) or died (without having regained consciousness) (CPC 5 in 11 pts) after a median (range) of 7 (1-23) days.

With serial determination, serum NSE concentrations of more than 70 ng/ml on at least two out of four days after resuscitation predicted a bad neurological outcome (CPC 4 or 5) with a sensitivity of 54%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 77%.

Conclusion: Serial determination of serum NSE concentration after cardiac arrest is highly predictive of neurological outcome.

717 Potential impact of public access defibrillators on overall survival following out of hospital cardiopulmonary arrest

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Background: Early defibrillation improves survival following cardiopulmonary arrest. Public access defibrillators are being provided in increasing numbers for use prior to the arrival of an ambulance. The aim of our study was to model the potential impact of public access defibrillators on overall survival.

Methods: Retrospective cohort study using the Heartstart register of all out of hospital cardiopulmonary arrests due to cardiac disease in Scotland over seven years. Within those arrest sites where public access defibrillators could potentially be located, it was assumed that survival among those waiting more than 3 min for ambulance attendance would be increased to that among those who waited 3 min or less.

Results: Of the 15,189 eligible arrests, 12,004 (79.0%) occurred in sites where public access defibrillators would be unlikely to impact on survival, 453 (3.0%) in sites where they may impact and 2732 (18.0%) in obvious sites for locating defibrillators. Defibrillation was undertaken in 67.9% of arrests that occurred in possibly suitable sites for locating public access defibrillators and 72.9% of those in definitely suitable sites. Overall survival increased from 744 (5.0%) to a predicted value of 942-959 (6.3%-6.5%) depending on the assumptions made regarding defibrillator coverage.

Conclusions: The predicted increase in survival from targeted provision of public access defibrillators is less than that achievable from expansion of first responder defibrillation or bystander cardiopulmonary resuscitation. Therefore, priority should be given to the latter. The additional resources required for very wide-scale coverage of public access defibrillators are probably not justified by the marginal improvement in predicted survival.

718 DEFI 77 PROJECT: out-of-hospital cardiac arrest in a French semi rural area. A prospective study

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Early defibrillation by the first attending caregivers is without any doubt the only care for a patient with ventricular fibrillation or pulseless ventricular tachycardia. In Seine et Marne area of France(1.19 million of inhabitants), the DEFI 77 PROJECT started in January 2001.Its purpose was to determine the location and incidence of cardiac arrest to plan the most efficient placement of Semi Automated External Defibrillator(SAED),and to implement a public training program.

The results of the first 13 months experience are shown: the number of SAED(n=18) given to the first aid non-medical team was multiplied by 7 in 2001 while more than 700 first-aid workers and firefighters were trained in the use of SAED.

During this period,the Mobile Intensive Care Units (MICU) and Firemen, covering a surface of 5915 km^2, treated 325 out-of-hospital cardiac arrest patients, 11% of which were in public locations.The majority of cases(88%)were due to presumed heart disease.Only 12.7% of bystanders initiated CPR.External defibrillators were used in 72 patients whose initial cardiac rhythm was VF/VT.The clinically relevant time intervals were a mean of 10 ± 6 minutes from call to arrival of the first-aid-team, 25 ± 20 minutes from collapse to the delivery of the first defibrillation shock...The mean age was 65 ± 16y;71% were male.

Among these patients, 73% received advanced cardiac life support by a physician deployed with MICU.11% were admitted alive to hospital, 2.8% had coronarography and 0.31% implantable cardioverter-defibrillator.Obviously,the survival rate (0.9% with good outcome)in this large area with a low density of population, but at less than 1 hour from Paris remains too much low particularly in comparison with those previously described in places like Seattle, planes, casinos...,assessing the current inability of community educational interventions to modify patients'survival.

So,the first part of DEFI 77 PROJECT suggest that a large gap remains between the goal of 20% survival's rate for all eligible patients presenting sudden cardiac death and present results. Therefore, this is justifying our efforts to strengthen the first steps of the chain of survival, in training of caregivers,and in a larger utilization of SAED.The results of the efforts will be evaluated in the second part of DEFI 77 Project.

719 Managing patients with life-threatening ventricular arrhythmias: the Leiden out of hospital cardiac arrest trial, LOHCAT

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Background: As ventricular arrhythmias (VA) are a major cause for sudden cardiac death, a careful evaluation is mandatory. Treatment is first aimed at elimination of reversible causes. Therefore, a systematic approach is necessary.

Methods: This prospective study evaluates the results of the LOHCAT protocol. From 1994 until 2000, 600 pts with life-threatening VA were included in this screening protocol, and data of these 600 pts will be presented at the meeting. The screening protocol includes: echocardiography, nuclear imaging, coronary angiography and EP study. In case the existence of arrythmogenic right ventricular cardiomyopathy (ARVC) was suspected, MR imaging was performed.

Results: Data from 444 consecutive pts (350 male, 59±13yrs), who were evaluated according to this protocol in the period 1994-2001 are presented in this abstract. Majority of them survived Ventricular Fibrillation (VF, n=235), the other pts had a (near) collaps due to Ventricular Tachycardia (VT, n=209). After screening, the underlying cause of these arrhythmias appeared to be previous myocardial infarction (MI) (n=242), acute MI (n=25), Idiopathic (n=50), Dilated Cardiomyopathy (n=50), Ischemia (n=29), Hypertrofic Cardiomyopathy (n=14), ARVC (n=14), congenital (n=12) and other causes (n=9). As a result of the screening protocol, pts underwent RF ablation of VT (n=63), ICD implantation (n=312), CABG (n=50), PTCA (n=45), and/or anti-arrhythmic drugs (n=227). More VT ablations were performed in the near collaps pts ($p<0.01$) than in the other group. During follow-up (26±24 months), a recurrence of VT/VF occurred in 93 pts (11 pts (17%) after RF ablation and 82 pts (26%) with an ICD, 6.5±10 shocks/pt, range 1-55). Thirty eight pts died (heart failure: 24, malignancy: 4, sepsis: 3, EMD: 3, recurrent VA: 2 and other: 2). One of them had an ICD, but unfortunately, there is no information available about the function of the ICD.

Conclusion: From these preliminary data, we conclude that a restricted ICD implantation strategy is appropriate, as only 2 pts died due to recurrent VT.

UPDATE ON CELLULAR EFFECTS OF LIPOPROTEINS

755 Impaired intravascular catabolism of chylomicron-like emulsions is a marker of clinical outcome in patients with stable angina

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Background: Despite evidence from case-control studies suggesting that chylomicrons and their remnants might directly enhance progression of coronary artery disease (CAD), data from longitudinal studies is lacking in order to confirm this hypothesis.
Methods and Results: Over a period of 4.5 ± 0.9 years, we followed 63 angiographically confirmed CAD patients (mean age 60.0 ± 10.0 years) in whom kinetic studies of the in vivo catabolism of chylomicron-like emulsions were performed. At enrollment into the study, fasting patients were injected intravenously with a chylomicron-like emulsion labeled with radioactive triglyceride (3H-TG) and cholesteryl esters (14C-CE) in order to determine the fractional clearance rate (FCR) of chylomicron-like particles. CAD patients displayed diminished FCR for 3H-TG (-26%;p=0.027) and 14C-CE (-37%;p=0.015) as compared with 35 control subjects (60.0 ± 10.0 years) without angiographically detectable CAD. In a multivariate logistic regression analysis, we found that FCR-CE was the only independent predictor of the presence of angiographically defined CAD. During follow-up, 21 CAD patients (33%) identified as the aggravating group (ACAD) presented refractory angina and increase of coronary angiographic severity. The remaining 42 CAD patients displayed a stable clinical evolution and were classified as the stable group (SCAD). Intravascular lipolysis and remnant removal from plasma of chylomicron-like emulsions, as expressed by the FCR for 3H-TG and 14C-CE, were significantly lower in the ACAD group as compared with that in the SCAD group.
Conclusion: This prospective study establishes that delayed intravascular turnover of triglyceride-rich chylomicron-like emulsions constitutes a predictive marker of the presence and outcome of CAD.

756 A novel oxidation product of 1-acyl-phosphatidylcholine, 1-stearoyl-2-azelaoyl-sn-glycerophosphocholine (SAzPC) induces platelet activation

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Platelet activation is a key step in acute coronary syndromes after plaque rupture leading to acute coronary thrombosis. Oxidized LDL contained in the plaque is thrombogenic. However, the platelet activating components of oxidized LDL are not yet fully identified. To further characterize platelet activating components of LDL, its major phospholipid species 1-acyl-phosphatidylcholine (PC) was studied.
One-stearoyl-2-arachidonoyl-PC was oxidized by CuCl2 and H2O2 and oxidation products were separated by high performance liquid chromatography and analyzed by electrospray mass spectrometry (ESI-MS). Platelet shape change was determined with an aggregometer and cytosolic free calcium was measured fluorometrically after loading of platelets with Fura-2.
Based on the molecular mass of m/z 694, the almost complete derivatization of the compound with pentafluorobenzyl bromide proving the existence of a free carboxy-terminal side chain and the typical fractionation pattern of the compound by ESI-MS/MS, revealed that one major oxidation product is 1-stearoyl-2-azelaoyl-PC (SazPC). SAzPC dose-dependently induced platelet shape change with a maximal concentration of 10 μM. Platelet shape change by SAzPC was not altered by inhibitors of the receptors for platelet-activating factor (PAF), lyso-phosphatidic acid or thromboxane A2. In contrast to PAF, SAzPC did not increase cytosolic free calcium concentrations in platelets.
These observations demonstrate that oxidation of 1-acyl-PC results in the formation of a highly bioactive compound, SAzPC, which activates human platelets. SAzPC may be involved in athero- and thrombogenic processes in vivo.

757 Cultured human coronary artery smooth muscle cells express the scavenger receptor glycoprotein IIIB (CD36)

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In the development of atherosclerotic plaques coronary artery smooth muscle cells (CA-SMC) change their phenotype from a contractile to a matrix secreting cell. Here we studied the effects of modified lipids on extracellular matrix synthesis of cultured CA-SMCs.
Methods: Human CA-SMCs (Clonetics) were used between passages 3-6. LDLs were isolated by sequential ultracentrifugation. LDL was oxidized in the presence of 5μM CuSO4 at 37°C for 24 h. Immunofluorescence microscopy was performed using cryosections of human coronary artery (CD36, iso-alpha-SM-actin) and cultured CA-SMC (CD36, iso-alpha-SM-actin, collagen types I and III and fibronectin).
c-fibronectin and collagen type I were measured by time-resolved fluorescence-immunoassay.DNA was quantified by fluorometry. Conventional and "real-time" RT-PCR was performed to measure the mRNAs of CD36, collagen I and III and fibronectin.
Results: Cultured human CA-SMC express the scavenger receptor glycoprotein IIIb (CD36). Foam cell formation was induced after addition of enzymatically (neuraminidase, cholesterol-esterase and trypsin) degraded LDL (eLDL) and VLDL (eVLDL) to cultured SMC (demonstrated by oil-red-O-staining and gas-chromatography of fatty acids after hydolysis of intracellular lipids). The CD36 blocking antibody OKM5 reduced uptake of fatty acids and foam cell formation. Oxidized LDL (oxLDL, 1-50μg/ml), malondialdehyde modified LDL (MDA-LDL, 1-50μg/ml), eLDL (1-10μg/ml) and eVLDL (0.1-4μg/ml) added to cultured SMC (4th - 7th passage) dose dependently increased the steady state levels of fibronectin- and collagen-mRNAs (within 8-12 h) and stimulated within 24 - 36h protein concentration of fibronectin and collagen type I in cell culture supernatants. Preincibation of the cells with OKM5 reduced the stimulatory effect of the modified lipids. Immunofluorescence demonstrated, that also cell associated collagen types I and III and fibronectin increased after addition of oxLDL, MDA-LDL, eLDL, oxVLDL and eVLDL to cultured MS-SMC. Higher concentrations of oxLDL (>50μg/ml), eLDL (>10μg/ml), oxVLDL (10μg/ml) and eVLDL (>4μg/ml) were cytotoxic.
Our data demonstrate that cultured human CA-SMC express the scavenger receptor CD36 which internalizes fatty acids and monoglycerides derived from enzymatically degraded LDL and VLDL forming hereby foam cells. Furthermore, oxLDL, MDA-LDL, eLDL and eVLDL stimulate the synthesis of extracellular matrix after binding to CD36.

758 Atherogenic levels of LDL downregulate vascular lysil oxidase gene expression: effect on endothelial cell permeability

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Background: Increase in vascular permeability associated to hypercholesterolemia is one of the earlier events in the atherosclerotic process. By differential display/RT-PCR we have identified lysil oxidase (LO) as a gene regulated by LDL in both human and porcine endothelial cells. LO is an enzyme involved in elastin and collagen crosslinking.
Objective: To analyze the molecular mechanisms involved in vascular LO downregulation and to assess the pathophysiological consequences of this effect in vitro and in vivo.
Methods: Quiescent porcine aortic endothelial cells (PAEC) or vascular smooth muscle cells (SMC) were incubated with increasing concentrations of LDL for 24 h. Pigs (Yorkshire-Albino, 32 ±4 kg) were randomized into two groups: normolipemic animals (n=6) which were fed with a normal chow (LDL-cholesterol: 35±10 mg/dL) and hyperlipidemic animals (n=10) which were fed with a cholesterol-rich diet for up to 100 days (LDL-cholesterol: 314±86 mg/dL). At this time animals have early/ mild atherosclerotic lesions (type I-II, AHA classification) in the arterial wall. LO mRNA levels in cell cultures and in porcine vessels were analyzed by RT-PCR. Endothelial permeability was determined by the exchange of fluorescein isothiocyanate(FITC)-dextran (Mr 40,000) in a Transwell" system. Signalling involved in this effect was analyzed using specific inhibitors.
Results: LDL (15 mg/dL, 24 h) decreased LO mRNA levels (3-fold) in porcine SMC. Interestingly, a similar decrease in LO expression (3-fold) was observed in vivo, in the vascular wall of hypercholesterolemic pigs ($p<0.01$). Moreover a strong and inverse correlation between plasma LDL concentrations and LO mRNA levels was observed ($p<0.001$ $r2=0.50$) suggesting a cause-effect relationship. Both nLDL (140 mg/dL) and an inhibitor of LO activity (b-aminopropionitril, 100 mM) increase FITC-dextran transfer through a endothelial monolayer. Pertussis toxin (protein Gi inhibitor), PD-098059 (MEK inhibitor) or SB-203580 (p38 MAPK inhibitor) did not block the effect of LDL.
Conclusions: Hypercholesterolemia downregulating vascular LO expression could modify extracellular matrix composition and vascular permeability. These changes could favor cellular and protein infiltration in the vessel wall, processes that are associated to the initiation and progression of atherosclerosis.

759 Lipoproteins differentially regulate the nuclear receptor Nor-1 in vascular cells

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Background: Lipoproteins play a key role in endothelial dysfunction and atherosclerosis. Recently we have shown that LDL induce expression of Nor-1, a member of the neural growth factor family of orphan receptors (NGFI-B family), in smooth muscle cells (SMC). These transcription factors seem to be involved in cell proliferation, differentation and apoptosis.
Objectives: To analyze the ability of lipoproteins (LDL and HDL) to modulate Nor-1 expression in vascular cells.
Methods: Porcine aortic endothelial cells (PAEC) and SMC were treated with LDL or HDL (from 5 to 60 mg protein/dL) and Nor-1 expression was analyzed by RT-PCR. The ability of lipoproteins to modulate Nor-1 transcription was assess by transfection assay. PAEC were transfected with a construct of Nor-1 promoter linked to luciferase using a liposome-based method (Lipofectin ®). 48 hours after transfection cells were expossed to lipoproteins (60 mg/dL) for 4 hours. The involvement of cAMP Response Element Binding Protein (CREB) in Nor-1 activation was analyzed by Electroforetic Mobility Shift Assay (EMSA) with the Nor-1 promoter cAMP response element (CRE). CREB activation was assessed by Western blot.
Results: LDL but not HDL strongly induced early Nor-1 expression in PAEC. LDL strongly induced (60.6 ± 11.9 - fold over controls) luciferase Nor-1 promoter dependent activity, while HDL did not produce significant effect (7.5 ± 3.2). EMSA results showed CREB binds to the CRE sequence present in the Nor-1 promoter. This effect was associated to an early (10 min) phosphorylation of CREB. In contrast, both LDL and HDL up-regulated Nor-1 mRNA levels in SMC.
Conclusions: LDL but not HDL induced Nor-1 expression in endothelial cells. Transfection assays suggest a transcriptional regulation of Nor-1 by LDL. Nor-1 seems to be involved in the genetic programs triggered by LDL in endothelium.

760 Modified lipoproteins reduce hepatocyte growth factor synthesis in human coronary artery smooth muscle cells

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Low density lipoproteins (LDL) are known to play a crucial pathophysiological role in the development and progression of atherosclerotic lesions. Hepatocyte growth factor (HGF) is a potent epithelial and endothelial cell regeneration factor which also seems to stimulate the activity of matrix metalloproteinases. This study aimed to investigate the influence of modified LDL and very low density lipoproteins (VLDL) on HGF synthesis in cultured human coronary artery smooth muscle cells (Clonetics, USA). LDL and VLDL were isolated by sequential ultracentrifugation, and LDL was oxidized by incubation with copper sulfate. LDL and VLDL were enzymatically degraded (eLDL, eVLDL; cholesterol esterase, trypsin, neuraminidase) and the increase in free fatty acid concentrations was quantified by gas chromatography. LDL and VLDL concentrations were referred to the protein content. HGF release into the cell culture supernatants was measured with a specific ELISA (R&D Systems, Germany) and HGF mRNA expression was evaluated by quantitative real-time RT-PCR using the LightCycler technology. Oxidized LDL (oxLDL 1-10 μg/ml), eLDL and eVLDL (0.1-2 μg/ml) as well as higher concentrations of native LDL (nLDL 10-100 μg/ml) induced a significant reduction of HGF release (minima: oxLDL 10 μg/ml 53.7±4.7%*** n=8, eLDL 58.3±0.9%* n=3, eVLDL 60.0±2.3%** n=6, nLDL 100 μg/ml 75.1±6.7%**, controls 100±5.1% n=10; means±SEM, *:p<.0.5, **:p<0.01, ***:p<0.001 versus control, 48 hours incubation). In parallel, a decrease of HGF mRNA expression was observed (oxLDL 1 μg/ml: 63.2±8.0%, nLDL 10 μg/ml: 70.3±6.4%, % of controls, n=11, 3-6 hours incubation). Furthermore, it was observed that nLDL was oxidatively modified by the cells during the incubation period and that higher oxLDL concentrations (20-100 μg/ml) exerted a cytotoxic effect, indicated by an increased LDH release and impaired cell viability. In summary, our data demonstrate that modified lipoproteins reduce HGF synthesis in cultured coronary artery smooth muscle cells. Presently, the role of HGF in atherosclerosis is unclear. HGF might have a protective effect by stimulating endothelial cell regeneration, on the other hand it also might promote atherogenesis and plaque instability by stimulating smooth muscle cell migration and by enhancing extracellular matrix degradation. The present findings suggest an interaction of lipoproteins and HGF in smooth muscle cells and might stimulate further studies to elucidate the role of HGF in coronary atherosclerosis.

ALTERED HEARTS HARBOUR ALTERED GENES

761 Disruption of dystrophin (D) and dystrophin-related proteins (DRP) is a trigger of advanced heart failure of both hereditary and acquired origins

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Background: We have reported that TO-2 hamster with DCM show gene mutation of delta (d)-sarcoglycan (SG) in DRP (Sakamoto et al., P.N.A.S., 1997), similar to human cases (Tsubata et al., J.Clin.Invest., 2000). D together with DRP stabilizes sarcolemma (SL) during the repeated SL expansion in systole and may require more resistance than skeletal muscle. In vivo transduction of recombinant adeno-associated virus (rAAV) vector with normal d-SG gene to TO-2 hearts induced long-lasting and efficient expressions of both transgene and transcript in myocardium and hemodynamics (Kawada et al., B.B.R.C., 2001). Most importantly, survival period of the animals was prolonged (Kawada et al., P.N.A.S., 2002). Acute heart failure (HF) model in rat by high-dose administration of isoproterenol induced translocation of D from SL to myoplasm but not d-SG degradation (Xi et al., J.Cardiovasc.Pharmacol., 2000). Thus, these results provide the hypothesis that HF of both hereditary and acquired origins is commonly caused by disruption of DRP or D.
Objective: To evaluate the contribution of DRP to the SL integrity, we examined the fine structure and stability of SL in cardiomyocytes of the TO-2 with or without the gene therapy. Furthermore, we evaluated the contribution of an endogenous protease, calpain, to the disruption of DRP.
Methods and Results: Double-stain of d-SG and D revealed co-localization of both proteins in SL of normal hearts, whereas TO-2 demonstrated D selectively. After the co-transduction of normal d-SG gene plus reporter (R) gene for 10 or 20 weeks, immuno-EM revealed patchy re-expression of transgene of d-SG along SL. The d-SG expression accompanied more intense staining of D than the case transfected by R gene alone. At 3 hours before sacrificing the animals, Evans blue (EB) was i.v. administered to identify membrane-degraded cells. The sustained transduction of d-SG reduced the cell area stained by EB after the gene therapy, denoting the improved SL stability. Incubation of both SL fraction and purified m-calpain from swine myocardium induced the proteolysis of D, alpha-, beta- and gamma-SG, but not d-SG in vitro the presence of Ca^{2+}.
Conclusion: These results indicate that SL degeneration would primarily induce the disruption of D or DRP by the endogenous protease and the lack of SL integrity is involved in the process of HF irrespective of the hereditary or acquired origins. Somatic gene therapy with potent rAAV vector would provide a new strategy for the treatment of advanced HF.

762 Changes in gene and protein expression for globins caused by mechanical decompression of the left ventricle through assist devices

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Reduced wall stress resulting from unloading of the left ventricle with a cardiac assist device in patients with heart failure leads to changes in gene and protein expression in the myocardium. However, comparison of myocardial specimens from 28 patients showed that the changes in gene expression differed to a great extent. No set of a fairly large number of gene expression changes could be detected for all the samples. This may be due to different loading conditions for the left ventricle, may be disease related, or may represent individual differences. Gene chip technology was applied (>6,000 genes) to look for differences in gene expression in the myocardium of six patients between the time of device placement and the time of transplantation. Protein expression was examined for substances with the most pronounced changes in gene expression. Gene expression for ANP and BNP showed a very pronounced reduction by a mean factor of 14.3 and 20.7, respectively, and many other genes showed changes of expression of mean factors below 9 (which were not rated for methodological reasons). Interestingly, gene expression for globin alpha, beta, and gamma was down-regulated by a mean factor of 9.5, 10.7, and 43.4, respectively. Similarly, protein proof in the specimens at the time of implantation was high and was significantly lower at the time of transplantation (reduction of the number of globin positive cells; mean factor of 8, 12, 34, respectively).
Application of chip technology resulted in the detection of a large number of changes of gene expression in the myocardial specimens between the time of device implantation and removal. However, only a small number of genes were up or down-regulated by factors above 9. The physiological significance of the existence of globins in the myocardium is not yet clear. Hypothetically, cells with globin may be differentiated from stem cells in the myocardium or the cells containing globin may be created due to a missing factor instead of myocytes.

763 Dysfunction of mitochondrial respiratory chain complex I in human failing myocardium is not based on disturbed mitochondrial gene expression

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Disturbance of mitochondrial gene expression by oxidative stress is discussed to be the reason for impaired mitochondrial function in ageing myocardium. The failing myocardium is assumed to be a form of premature myocardial ageing and disturbances of mitochondrial gene expression have been observed in experimental myocardial failure. For this reason we investigated in human left ventricular myocardium of explanted terminally failing hearts (31 DCM, 12 ICM) and in 12 donor hearts enzyme activity of respiratory chain complexes (C) with mitochondrial encoded subunits (C-I, C-III, C-IV) in comparison with the activity of the exclusively nuclear encoded C-II. In addition mRNA expression of mitochondrial encoded genes was compared with nuclear encoded mitochondrial components.

In 43 explanted ventricles, the citrate synthase related enzyme activity of C-I (11,47±0,81 a.U.) was smaller than in 12 donor hearts (15,92±1,51 a.U.; DCM~ICM; $p<0,001$), whereas that of C-II was identically (19,21±1,82 vs. 18,36±1,01 in donors). At the first glance this appears in agreement with the hypothesis of disturbed mitochondrial gene expression, which predicts that complexes with mitochondrially encoded subunits (C-I) are disturbed in contrast to complexes with only nuclearly encoded subunits. However, the mRNA expression values showed neither for the mitochondrial encoded genes(ND1, ND2, ND3, ND4, ND4L, ND5, ND6, cytochrome b, COX-I, COX-III, 16S rRNA; semiquantitative RT-PCR controlled by Northern blot)nor for the MnSOD (nuclear encoded) significant differences, whereas mRNA of TNF-alpha (0,21±0,02 vs. 0,15±0,01; $p< 0,05$) and of Pro-ANP (0,63±0,15 vs. 0,15±0,06; $p<0,005$)was significant higher in explanted failing ventricles. The enzyme activity of C-III und C-IV in explanted failing ventricles, the intact mitochondrial wildtype DNA (Southern blot) and the protein expression of the nuclear encoded mitochondrial transcription factor (mtTFA; Western blot) were unchanged compared to donor organs.

We conclude that the observed selective reduction of the C-I enzyme activity in the failing human myocardium is not a consequence of a disturbed mitochondrial gene expression, but probably the result of an altered assembling of the macro complex.

764 The EDG-receptors are functional in human fibroblasts and are regulated in human heart failure

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The phospholipids lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P) affect cell proliferation, survival during hypoxia, cytoskeleton architecture and embryonic development in rodent hearts. Their effects are mediated by a family of G-protein coupled receptors encoded by endothelial differentiation genes (EDG). These receptors bind LPA (EDG-2,-4,-7) or S1P (EDG-1,-3,-5,-6,-8) and act via Gq, G12/13 and Gi. Their presence has been demonstrated in rodent hearts, but not yet in human hearts. We determined their presence in the human heart, regulation in human cardiac disease and functionality in human fibroblasts.

In the first set of experiments, the expression of EDG-1,-2,-3,-4,-5 and -7 mRNA was assessed in human myocardial samples and in HT1080 cells, a human fibroblast cell line, by PCR and sequencing. In the next step, the mRNA for EDG-1 and -2 was quantitated by real-time PCR (PE 5700) in left ventricular samples taken during aortic valve surgery from patients with aortic valve stenosis (AS, LV EF: 44 ± 6%) and from explanted hearts with ischemic (ICM, n=7) and dilated cardiomyopathy (DCM, n=27) and in 15 controls (unused donor hearts with normal systolic function) after informed consent and agreement of an ethical committee. EDG mRNA was related to the stably expressed GAPDH mRNA. To analyse the effects of LPA and S1P on human fibroblasts, HT1080 cells were stimulated for 6h with 100 nM LPA or S1P and the activity of matrix-metalloproteinases (MMPs) was analysed by gelatine-zymography.

EDG-1,-2,-3,-5 and -7 were found in human myocardium and EDG-1,-2,-4,-5 and -7 in HT1080 fibroblasts. EDG-1 was significantly upregulated in DCM (200% of control, $p<0.05$), in ICM (216%, $p<0.01$), and AS (175%, $p<0.002$). EDG-2 was unchanged in DCM (159%, ns) and increased in ICM (198%, $p<0.05$) and AS (247%, $p<0.05$). In HT1080 cells, EDGs contributed to the regulation of matrix-metalloproteinases proMMP2, MMP2 and MMP9. Stimulation with S1P upregulated the activity of proMMP2, MMP2 and MMP9. Stimulation with LPA led to downregulation of the activity of these MMPs.

These results suggest that the EDG-receptors, particularly EDG-1 and -2, are present in the human heart and are regulated in human heart disease and may contribute to the control of extracellular matrix turnover in human fibroblasts.

765 Beta-sarcoglycan gene mutations cause plasma membrane dysruption in striated and smooth muscle, leading to severe dilated cardiomyopathy

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Background: The sarcoglycan (SG) complex (alfa-, beta-, gamma-, and delta-SG) is a component of the structural proteins localized to the plasma membrane of striated muscle, where it confers mechanical stability during muscle contraction. SG gene mutations cause limb-girdle muscular dystrophies (LGMD), but only rarely the myopathy is associated with overt cardiac involvement.

Material and Methods: We studied 4 patients (aged from 9 to 37 years, 2 males, t2 females) with beta-SG gene mutations and muscular dystrophy, to verify the presence of cardiomyopathy. The diagnosis was performed by skeletal muscle biopsy, SG proteins (immunohistochemistry, western blot) and genes analysis (SSCP, DNA sequence), ECG, 2D and Doppler echo-cardiography.

Results: All patients suffered from severe muscular dystrophy. Beta-SG gene mutations were small frameshift deletions, insertions or duplications (5/8 mutant alleles), missense mutations (2/8 alleles), and one nonsense mutation. Mutations in the beta-sarcoglycan gene caused the loss of the entire SG complex in the skeletal muscle with a consequent plasmalemmal damage and fiber necrosis. 2 patients (50%) showed cardiac involvement. Left ventricular (LV) diffuse hypokinesia (EF=38%) was present in one patient and biventricular severe dilatation and reduction of ejection fraction (LVEDV=118 ml/m^2, LVEF=32%) in the second patient, who died from cardiac failure at age 14 years.

Sex,age	LVEDV (ml/m^2)	LVEF (%)	Clinical phenotype	Gene mutations
M, 14 *	118	32	severe LGMD, DCMP, HF	4bp del.,8bp ins.
F, 9	66	53	severe LGMD	8bp ins., nonsense
F, 20	58	55	severe LGMD	missense homoz.
M, 37	67	38	LGMD, LV hypokinesia	32bp dupl.homoz.

Discussion: Since the SGs are expressed in striated muscle, SG gene mutations are expected to affect both the skeletal and cardiac muscle, due to the loss of structural and functional plasma membrane integrity. We demostrated that mutations in the beta-SG gene are a common cause of dilated cardiomyopathy. Unlike other SGs, beta-SG is additionally expressed in smooth muscle of the coronary vessels, thus a perturbation of vascular function would represent an additional mechanism. In the future, study of the coronary reserve may shed light on the pathogenesis of cardiomyopathy; in addition, pharmacological treatment with vasodilators merits further investigations as a potential therapeutic option.

766 Significant structural alterations in the mitochondrial D-loop control region may occur in cardiomyopathy

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Damage in mitochondrial DNA (mtDNA) coding genes and reduced bioenergetic generation has been previously reported in human cardiac tissues with aging and in selected cardiac disorders. An age-dependent accumulation of point mutations in the non-coding control region of human mitochondrial D-loop has been recently found in cultured fibroblasts and skeletal muscle cells; whether these changes occur in cardiac tissue is unclear. Accordingly, we undertook the current study to examine mtDNA D-loop region in a series of patients with cardiomyopathy (CM) and normal controls. Also, the effect of age was evaluated.

Methods: We analyzed cardiac mtDNA for the incidence and distribution of point mutations in the D-loop control region involved in mtDNA replication and transcription (from 110-570 nt) in 47 patients with CM and 40 subjects with no history of cardiac disease. Frequency and distribution of mutations in relation to age, and cardiac disease were assessed, and compared to changes in a cytb fragment of roughly the same size in controls and patients.

Results: A total of 118 homoplasmic point mutations were found at 30 positions in patients with CM compared with 111 mutations at 34 positions in controls. However, mutations in important regulatory sites within the D-loop control region (including mtTFA sites and the conserved sequence blocks) were present in 8 patients (17%) and not found in controls. Patients with a combination of two of these alleles (n=3) have a more marked phenotype of mitochondrial dysfunction including both reduction in multiple respiratory enzyme activities and marked reductions in the level of cardiac mtDNA. No significant accumulation of point mutations in the D-loop control region or in cytb was found as a function of age.

Conclusion: Specific mutations at critical sites in the D-loop were found in CM and they were associated with significant respiratory enzyme defects. The combination of mutations and defective bioenergetics may play a pathogenetic role in a subset of patients. Contrary to findings in cultured fibroblasts and skeletal muscle cells age does not appear to be a factor in the accumulation of cardiac mtDNA D-loop mutations

REPERFUSION INJURY DURING CARDIAC SURGERY

771 Reperfusion after open heart surgery is the most damaging factor for myocardial tissue

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Aim: To assess ultrastructural changes of myocardial capillaries and cardiomyocytes due to ischemia and reperfusion during open heart surgery.
Methods: We evaluated 61 consecutive patients (pts) who underwent open heart surgery. 215 byoptical samples were taken from right ventricle anterior wall, and from the apical region. They were taken during ischemic pctiod (5,10, 20, 30 min starting cardioplegia (CPL), and at the end of CPL) and during reperfusion period (5-30 mm after beginning of this period). All samples were analyzed by electron microscope using quantitative stereological analysis. Volume fraction of the pinocite vesicles (PV), mitochondria (M), and endoplasmatic reticulum (EPR) were calculated. All pts were devided into 2 groups based on duration of CPL - ischemia; group 1 (CPL <65 min., 19 pts), and group 2 (CPL>65 mm, 42 pts).
Results: Damages of the endothelial cells and cardiomyocytes in all samples occurred 5 minutes after introduction of CPL and progressively increased during ischemic phase. The worse damage was found after 65 mm. of CPL usage: capillaries obstruction due to microclasmatosis, edema of the endothelial cells, widening of the cell junctions, degenerative changes of the cardiomyocytes. Stereological analysis confirmed that the larger damages were found during reperfusion in group 2 (table).

	Group I			Group II		
Variable	ischemia	reperfusion	p	ischemia	reperfusion	p
PV(Vv)	0.052	0.043	<0.05	0.033	0.028	<0.01
MV(Vm)	0.024	0.025	NS	0.022	0.017	<0.01
EPR(Vr)	0.026	0.026	NS	0.025	0.023	<0.01

Conclusion: Cells of myocardium are very sensitive to hypothermia, hypoxia and reperfusion during open heart surgery. Ultrastructural changes of endothelium and cardiomyocytes depend on the length of CPL usage time, and are particularly induced by reperfusion.

772 Insufficient protection of the conduction system during cardioplegic arrest – Necrosis but not apoptosis

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Background: Conduction system disturbances after cardioplegic arrest remain an unsolved problem. We investigated whether ischemia/reperfusion injury due to cardioplegic arrest contributes to myocardial conduction cell (MCC) necrosis or apoptosis and whether MCC react differently from working myocardial cells (WM).
Methods: Under cardiopulmonary bypass conditions minipigs were subjected to 60 min. of crystalloid cold antegrade intermittent cardioplegic arrest followed by 180 min. of reperfusion (n=20). Hearts not subjected to any procedure served as controls (n=5). Subendocardial MCC and adjacent WM from the LV free wall and the RV septomarginal band were investigated histologically. HE and immunohistochemical staining for apoptosis-associated proteins (bax, bcl-2, CPP-32) was performed. DNA-breaks were visualized by TdT-mediated dUTP-biotin nick end labeling (TUNEL). Electron microscopy was performed in order to differentiate between apoptosis and necrosis.
Results: MCC of control animals constitutionally expressed bax, bcl-2, and CPP-32. After cardioplegic arrest with reperfusion, marked reduction of apoptosis-associated protein labeling was focally found in subendocardial MCC (15/20 hearts; Fig.1). In 6.3%±6.4 of subendocardial MCC, karyopycnosis and increased eosinophilia (HE) were observed. Positive TUNEL-staining was found in 2,8%±2,5 of subendocardial MCC. The average TUNEL-rate of the adjacent WM was < 0,1%. Electron microscopy demonstrated ischemic changes in MCC consistent with cellular necrosis.

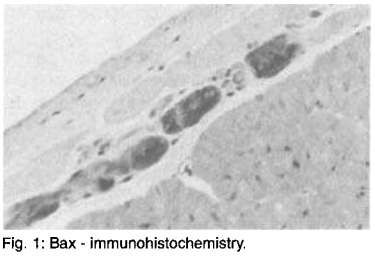

Fig. 1: Bax - immunohistochemistry.

Conclusion: Ischemia and reperfusion injury due to cardioplegic arrest leads to significant subendocardial MCC damage, far exceeding damage of the WM. Ultrastructural and light-microscopic findings are consistent with coagulation necrosis, rather than apoptosis.

773 Inhibition of IkBa phosphorylation with BAY 11-7085 attenuates myocardial reperfusion injury in rabbits

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Myocardial reperfusion injury has been attributed to neutrophil released mediators like oxygen derived free radicals, cytokine syntheis, loss of endogenous nitric oxide and increased neutrophil accumulation. Subsequent cellular activation with translocation of NFkB, transcription initiation, and synthesis of inflammatory molecules like TNFa, IL-6 and ICAM-1 will occur.
We studied the effect of BAY 11-7085, known to inhibit phosphorylation of IkBa following TNFa stimulation, in vivo in a rabbit myocardial reperfusion injury model (60 minutes ischemia followed by 3 hours reperfusion). BAY 11-7085 (0,2mg/kg) or its vehicle were injected 5 minutes prior to reperfusion. Myocardial injury following BAY 11-7085 treatment was significantly reduced compared to vehicle treated animals (16%±2.1% vs 32.6%±1.8% necrosis related to ischemic myocardium, $p<0.05$). Plasma creatine kinase (CK) activity, another marker for myocardial injury increased from 4.5±0.4 IU/g protein at baseline to 55.3±3.3 IU/g protein following 3 hours of reperfusion in the vehicle group. Administration of BAY 11-7085 significantly decreased plasma CK release throughout the reperfusion period (31.8±1.5 IU/g protein, $p<0.05$). In the necrotic zone myeloperoxidase (MPO) activity, a marker for polymorphonuclear leukocyte (PMN) accumulation, was significantly decreased in BAY 11-7085 treated animals compared to the vehicle group ($p<0.01$). Histologic analysis of ischemic reperfused myocardium of vehicle treated animals showed 56±6 PMN/mm^2. BAY 11-7085 treatment resulted in a significant reduction of neutrophil accumulation in the reperfused myocardium (28±5 PMN/mm^2, $p<0.01$). In vitro adhesion assays demonstrated reduced PMN adherence to ischmic reperfused arteries following BAY 11-7085 treatment. Similar, BAY 11-7085 significantly reduced PMN adherence to TNF-a activated vascular endothelium. Further, BAY 11-7085 inhibited NFkB translocation in vascular endothelial cells following TNF-a stimulation
Thus, blocking of phosphorylation of IkBa with BAY 11-7085 appears to be an effective mean to preserve ischemic myocardium from injury following reperfusion. The cardioprotective effect appears to be at least in part due to reduced PMN adhesion and infiltration with subsequent diminished myocardial necrosis.

774 Poly-ADP-ribose polymerase (PARP)-inhibition protects against myocardial and endothelial reperfusion injury after hypothermic cardiac arrest

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Free radical production and related cytotoxicity during ischemia/reperfusion may lead to DNA strand-breakage which activates the nuclear enzyme poly-ADP-ribose synthetase (PARP) and initiates an energy consuming, inefficient repair cycle, with transfer of the ADP-ribosyl moiety of NAD+ to protein acceptors. We investigated the effects of PARP inhibition on myocardial and endothelial function during reperfusion in an experimental model of cardiopulmonary bypass
Twelve anesthetized dogs, underwent hypothermic cardiopulmonary bypass. After 60 minutes of hypothermic cardiac arrest, reperfusion was started after application of either saline vehicle (control, n=6), or PJ34 (10 mg/kg) a selective PARP-inhibitor (n=6). Left ventricular hemodynamic variables were measured by a combined pressure-volume-conductance catheter and the slope of the end-systolic pressure volume relationship (Ees) was calculated at baseline and after 60 minutes of reperfusion. Left anterior descendent coronary blood flow (CBF), endothelium-dependent vasodilatation to acetylcholine (ACH) and endothelium-independent vasodilatation to sodium nitroprusside (SNP) were also determined.
The admimistration of PJ34 led to a significantly better recovery (given as percent of baseline) of left ventricular systolic function (dP/dt: 61±7% vs. 38±10%, $p<0.05$ and Ees 67±6% vs. 46±6%, $p<0.05$). CBF was also significantly higher in PJ34 group (32±4 vs. 21±3, ml/min, $p<0.05$). While the vasodilatatory response to SNP was similar in both groups, ACH resulted in a significantly higher increase in CBF in the PJ34 group (59±10% vs. 28±15%, $p<0.05$).
PARP inhibition improves the recovery of myocardial and endothelial function after cardiopulmonary bypass with hypothermic cardiac arrest.

775 Immunomodulator rapamycin attenuates myocardial reperfusion injury in rabbits

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Myocardial reperfusion injury has been attributed to increased neutrophi accumulation with inflammatory injury. Cellualr adhesion and cytokines exert protein synthesis in the ischemic reperfused heart. The precise role of rapamycin in ischemia reperfusion is unknown.

We studied the effect of the immuno-suppressor/-modulator Rapamycin (Rapa) in vivo in a rabbit myocardial reperfusion injury model (60 minutes ischemia followed by 3 hours reperfusion). Rapa (1μg/kg) or its vehicle were injected 5 minutes prior to reperfusion. Myocardial injury following Rapa treatment was significantly reduced compared to vehicle treated animals (15%±3% vs 32%±2% necrosis related to ischemic myocardium, $p<0.05$). Plasma creatine kinase (CK) activity, another marker for myocardial injury increased from 2 ±0.2 IU/g protein at baseline to 36±3.3 IU/g protein following 3 hours of reperfusion in the vehicle group. Administration of Rapa significantly decreased plasma CK release throughout the reperfusion period (15±2 IU/g protein, $p<0.05$). In the necrotic zone myeloperoxidase (MPO) activity, a marker for polymorphonuclear leukocyte (PMN) accumulation, was significantly decreased in Rapa treated animals compared to the vehicle group ($p<0.01$). Histologic analysis of ischemic reperfused myocardium of vehicle treated animals showed 75±8 PMN/mm^2. Rapa treatment resulted in a significant reduction of neutrophil accumulation in the reperfused myocardium (33±5 PMN/mm^2, $p<0.01$). With proteome analysis we were able to demonstrate differences in protein expression following Rapa treatment (i.e. preserved expression of superoxide dismutase and heat shock protein).

Thus, blocking of translation with rapamycin appears to be an effective mean to preserve ischemic myocardium from injury following reperfusion. The cardioprotective effect appears to be at least in part due to preserved protein expression with subsequent reduction of PMN accumulation and myocardial necrosis.

776 Deferoxamine cardioplegia improves mitochondrial morphology in human myocardium

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Enhanced myocardial protection during ischemia using the oxygen free radical deferoxamine has been demonstrated experimentally and clinically. Mitochondria have marked functional and morphologic abnormalities and are very sensitive to ischemic damage. This study aimed at determining whether deferoxamine has a protective effect by preserving the morphology of mitochondria in human myocardium after ischemia-reperfusion.

Methods: Patients (pts) who underwent elective first-time operation of the aortic, mitral, or both valves were included in the study. They were randomly allocated to either St. Thomas? cardioplegic solution (group A) or cardioplegic solution supplemented with deferoxamine (group B).

Myocardial biopsy specimens were obtained from the sub-endocardial layer and were immersed immediately in gloutaraldeyde solution. After special processing, mitochondrial morphology was determined by electron microscopy x62,500. The severity of mitochondrial damage was graded as follows: 0=normal mitochondria, 1=swelling without architectural disruption and 2=architectural disruption. 154 mitochondria from group A (7 pts) and 281 from group B (7 pts) were included in the study. Student's t-test was used to analyze the data.

Results: There was a continuing improvement of mitochondrial morphology in all grades as presented in the table.

Severity of mitochondrial damage

	Group A	Group B	p
Grade O	15 (9.8%)	255 (90.8%)	<0.0001
Grade 1	106 (68.8%)	26 (9.2%)	<0.0001
Grade 2	33 (21.4%)	0	<0.0001
Total	154	281	

Conclusion: Deferoxamine appears to have a moderating effect on mitochondrial morphology in ischemia-reperfusion injury.

CAROTID STENTING

777 Routine use of cerebral protection during carotid artery stent implantation: procedural results of a multicenter registry of 692 procedures

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Background: Cerebral protection devices are used during percutaneous carotid artery stenting to reduce distal embolization of debris, which may result in neurological deficit.

Methods and Results: 692 consecutive procedures (645 patients) of elective carotid stent implantation using cerebral protection performed in 5 different centers were included in a prospective registry.

Cerebral protection was attempted using filter devices (73.8% of procedures), occlusive distal balloons (23.6%), and endoluminal clamping of the common and external carotid artery (2.5%).

All lesions presented a >70% diameter stenoses (mean 80±9%). Mean age of the patients was 70±12 years, 83.2% were males, and 51.0% of patients had a previous, hemisphere related, stroke or transient ischemic attack. In 653 procedures (96.4%) it was possible to position a protection device. In 13 of 164 procedures with distal balloon protection, this was not tolerated by the patient (6.3%). In 683 procedures (98.7%) a stent was successfully placed. Neurological complications during the procedure, in-hospital and during 30 days of follow-up occurred after 36 procedures (5.2%). These were 5 major strokes (0.7%), 14 minor strokes (2.0%), 12 transient ischemic attacks (1.7%), 1 embolization of the retinal artery (0.1%), and 5 intracerebral haemorrhages (0.7%) of which 4 were without clinical sequels and 1 leading to myocardial infarction and death. Protection device related complications, all without neurological symptoms, occurred in 8 procedures (1.1%). These were 7 distal dissections of which 3 were covered with additional stents, 1 leading to occlusion of the internal carotid artery, and 1 filter entrapment requiring surgical removal. Major adverse cardiac events (MACE) during the 30 days of follow-up occurred in 3 patients (0.4%) and were 2 fatal and 1 non-fatal myocardial infarctions. Combined minor/major stroke rate was 2.7%, combined stroke/death rate was 2.9%, and combined stroke/MACE/death rate was 3.0%.

Conclusions: Routine cerebral protection during carotid artery stenting appears feasible and safe. In the present registry the incidence of stroke was low.

778 Emergency stenting for stroke after carotid endo arterectomy

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Background: Carotid endoarterectomy (CEA) has been established as the standard treatment for carotid occlusive disease and has been shown to be beneficial in patients with high-grade carotid stenosis. Nevertheless this approach is not free of complications. Among these, perioperative stroke and death have been reported in 2.5-7.5% but the incidence can be as high as 18% in the high risk-patients. The management of perioperative neurological deficits complicating CEA is still controversial. We report immediate and long term result of emergency carotid stenting for stroke complicating CEA.

Methods and Results: From April 1998 to July 2001, 25 patients underwent emergency carotid angioplasty and stenting for perioperative stroke. Among all procedures, 21 were performed in the hemodynamic laboratory and the remaining 4 in the operating theatre. Carotid angiography was performed immediately (within 15 ± 5 min) after the appearance of neurological symptoms. Thrombosis at the CEA site was found in18 (72%) lesions and vessel dissection in the remaining 7 lesions (28%). Adjunctive carotid artery angioplasty with direct stent implantation was performed in all patients (within 35 ± 12 min) with a technical success rate of 100%. 3 (12%) deaths occurred in hospital, all related to neurological events (within 15 days). At a mean follow-up of 14 ± 9 months (rang 1 to 28) 1 (4%) death occurred after 3 months, not related to cerebral event. One patient (4%) had incomplete recovery. Complete neurological status recovery was observed in 21 patients (84%).

Conclusions: Emergency percutaneous transluminal angioplasty carotid stenting (PTACS) is feasible, safe and effective in the treatment of perioperative stroke after CEA leading to a complete neurological recovery in the majority of the patients.

779 Predictors of adverse events and impact of the learning curve in the carotid angioplasty and stenting free of emboli (CAFE) USA trial

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Background: Distal protection devices reduce the occurrence of periprocedural events in pts undergoing carotid artery stenting (CAS). The determinants of adverse neurologic events during CAS with "neuroprotection", and the impact of the learning curve are unknown.
Methods: CAFE-USA was a multicenter prospective registry that evaluated the utility of the PercuSurge GuardWire (GW) balloon occlusion and aspiration system in 212 consecutive pts undergoing CAS. To evaluate learning curve issues, outcomes in the first 106 pts (Group I) were compared to the last 106 pts (Group II). The CREST trial definitions were used for all events.
Results: Mean age was 72 ± 8 years; 66.5% were male. Most high-risk baseline features were equally prevalent in the 2 groups, though bilateral disease (63.2% vs. 48.1%, p=0.02) and history of CEA (20.8% vs. 8.5%, p=0.01) were more common in group I.

Procedural results

	Group I	Group II	P-value
Successful GW placement	93.4%	95.3%	0.55
Duration of balloon occlusion (min)	12.9 + 6.0	10.7 + 3.2	0.001
Total procedure time (min)	78 + 47	65 + 30	0.01
Contrast used (ml)	180 + 79	152 + 74	0.008
Hypotension post-CAS	27%	14%	0.02
Embolic stroke	1.9%	0.9%	1.0
Cummulative 30 day events:			
Neuro-death	2.7%	1.4%	1.0
Non-disabling stroke	4.9%	3.1%	0.72
Any neurologic event	7.6%	4.5%	0.44

By logistic regression analysis, GP IIb/IIIa inhibitor use (OR=8.17, p=0.02), prior stroke (OR=4.7, p=0.02), and prior MI (OR=4.52, p=0.02), were independent predictors of 30-day adverse events.
Conclusions: During CAS with neuroprotection, embolic stroke is extremely rare and appears to decrease overtime with experience. Patient selection baseline characteristics, and adjunct pharmacotherapy (NOT embolic events) drive the event rate in the CAS with neuroprotection.

780 White blood cell count predicts microembolic Doppler signals during carotid stenting: a link between inflammation and embolization

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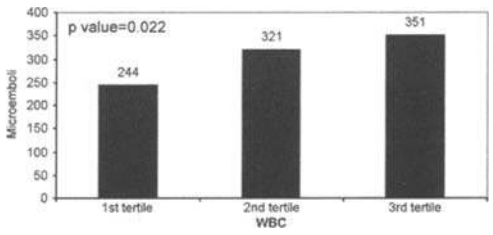
Background: A number of inflammatory markers, including white blood cell (WBC) count, predict clinical outcome in patients with atherosclerotic vascular disease. It has been hypothesized that the degree of systemic inflammation is related to the propensity toward atheroembolization, however this theory remains unproved.
Methods: We examined 46 consecutive patients who underwent a transcranial Doppler (TCD) examination of the ipsilateral middle cerebral artery during elective carotid stenting at our institution between 4/98 and 6/01. TCD offers real-time in vivo measurement of cerebral embolization. High intensity transient signals (HITS) recorded on TCD during wire manipulation, balloon pre-dilation and stenting were summed for each patient (1 second shower counted as 10 microemboli). Stepwise multiple linear regression was used to identify independent predictors of microembolization.
Results: In the overall cohort (median age 72, 74% male, 87% CAD, 24% diabetes, emboli protection device use 15%) median pre-procedure WBC count was 7.2 (interquartile range [IQR] 6.2-8.6) and median total HITS was 305 (IQR 217-402). Microembolization increased significantly in each successive WBC tertile [Figure]. After adjusting for age, gender, comorbidities, concomitant medical therapies and the use of emboli protection devices, increasing WBC count remained a significant and independent positive predictor of embolization (beta 38.4, standard error 14.6, p=0.012).
Conclusion: These data provide further support for an association between the degree of systemic inflammation and subsequent atheroembolization during percutaneous intervention. Other markers of inflammation should be evaluated in this setting.



781 Carotid angioplasty using coronary angioplasty equipment: acute results and long-term follow-up

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Introduction: Since February 1994, we treated 226 high-grade lesions of the internal carotid artery in 205 patients using coronary angioplasty equipment. In 146 lesions one of the following embolic protection devices was used: Percusurge in 46, Angioguard filter in 23, Arteria in 34, EPI filter in 19, TRAP in 14, Mednova in 7, MO.MA in 3. 62 Carotid Wall stents, 83 self-expending Nitinol stents and 98 balloon expandable stents where implanted. Follow-up investigations included a neurological examination and duplex ultrasound after 6 and 12 months, thereafter annually.
Results: The patients age ranged from 40- 88 years with an average of 70 ± 9 years. 122 lesions were asymptomatic, 104 symptomatic. 117 patients had a contralateral stenosis or occlusion and 47 patients additional vertebral or intracranial lesions. 67% of the patients suffered from coronary heart disease,65% from hypertension, 30,5% from diabetes mellitus, 43% from hyperlipidemia and 52% were previous or current smokers.
The procedure was technically successful in 224/226 lesions. 10 patients had one of the following acute or subacute (<30 days) complications: Cerebrovascular death in 0, non-fatal major stroke in 3, minor stroke in 1, central retinal artery occlusion in 1, asymptomatic occlusion in 1, non-cerebrovascular death in 4 patients. Follow-up investigations were performed after 6 and 12 months, thereafter annually up to 100 months, in average 17 ± 20 months after the procedure 128/205 patients (=128/226 lesions) had a 6 months follow-up. During follow-up (311 patient years) 4 major, 2 minor strokes and 16 asymptomatic re-stenoses occurred. 17 patients died from non-cerebral causes.
Conclusion: Carotid angioplasty and stenting using coronary angioplasty equipment and embolic protection devices leads to results which are at least comparable to the results of endarterectomy. Re-stenoses and late complications are rare.

782 Carotid stenting in high risk patients – a single center experience

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Background: Carotid artery stenting (CAS) is emerging as a new alternative treatment for carotid artery stenosis.
Aim: To review our initial experience with this technique, using self-expanding stents in selected high risk and post carotid endatherectomy (CEA) restenosis patients.
Methods: 51 procedures in 47 patients were performed between April 1998 and November 2001. Our technique included the use of long femoral sheaths for carotid access and stent deployment. All patients underwent Duplex study before the procedure. Criteria for treatment was presence of stenosis >70% by angiography. Clinical follow-up was performed at 1, 3, and 6 and 12 months from the procedure and carotid duplex scan was performed at 3 months and one year. Endpoints were death, CVA, and target vessel revascularization during hospitalization and at follow-up period. Distal protection devices were used in 8 procedures. Transcranial Doppler was measured during the procedures in 23 patients.
Results: Mean age was 70 years (range 56 to 81) with 66% males. The indication for CAS was restenosis after CEA in 35 procedures, distorted neck anatomy in 6, and severe IHD in 13. The procedure was successful in 48 cases, while in 3 procedures the wire could not cross the lesion. In hospital complications included one death due to intracranial hemorrhage, and 2 TIA's. At 1-month follow-up (n=42) there were no additional events. At 1 year (n=20) 1 patient had a minor stroke and six patients had asymptomatic restenosis by Duplex. One patient underwent angiography and balloon angioplasty due to restenosis of 90%. Another patient who was asymptomatic had stenosis of 100% that we decided not to treat. And the other four patients the stenosis was 50-70%, all asymptomatic and we decided on conservative treatment and follow-up. TCD results show multiple microemboli during the procedure with peak at balloon deflations. However they were clinically silent.
Conclusions: Our initial experience shows that CAS is a safe method in high surgical risk and post CEA patients. The potential of distal protection devices for increasing the safety of the procedure will be answered by future studies.

IMAGING THE CORONARY ARTERY: ARE THE NEW TECHNIQUES COMPETITORS OR ADJUNCTS TO ANGIOGRAPHY?

783 Noninvasive measurement of diameter of the distal left anterior descending artery by thoracic echocardiography with a 10MHz transducer

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Background: Transthoracic Doppler echocardiography provides information about coronary flow velocity in the left anterior descending artery (LAD) noninvasively. It was difficult to obtain the image of vessel wall due to the quality of two dimensional echocardiocardiography.
High frequency(10MHz) two-dimensional echocardiography allows visualization of the distal LAD.
Method: we evaluated 32 pts (14 myocardial infarction, 18 angina pectoris) using a commercially available VIVID 7 echograph(GE Yokogawa medical)
Distal LAD was imaged transectionally and longitudinally under the guidance of color flow mapping. At the region of maximal width of color flow mapping in the LAD, the vessel wall were imaged and diameter of LAD were measured.
We compared diameter of the distal LAD by echocardiography with diameter obtained by quantitative coronary angiogram.
Results: In 24 out of 32patients (75%), imaging of diatal LAD was obtained.
There were close correlations between transthoracic echocardiography and coronary angiographycal methods for measurement of diamter of the distal LAD (r=0.91, y=0.95x+0.1)
Conclusion: Noninvasive measurement of diameter of the distal LAD using a10MHz high frequency transducer accurately reflects invasive measurement of diameter of the distal LAD by coronary angiographycal method. Thus this method can provide useful information about the change of diamter of LAD under various conditions.

784 Effect of plaque debulking before stent implantation on in-stent neointimal proliferation: serial three-dimensional IVUS analysis

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Objectives: We report volumetric assessment of neointimal formation by three-dimensional intravascular ultrasound (IVUS) analysis, comparing primary stenting with adjunctive stenting following plaque removal with directional coronary atherectomy (DCA).
Background: Recent IVUS studies suggest a role for plaque burden in promoting neointimal hyperplasia after stenting.
Methods: Twenty-four patients (24 lesions) receiving DCA before stenting were matched to 24 patients (24 lesions) who underwent stenting without DCA in the same period. All used stents were a single Multilink stent (15 mm long only). Serial IVUS was performed before and after intervention and at 6-month follow-up. The same arterial segments as the stented segments on serial studies were analyzed using a computer based contour detection program. The following measurements were obtained: (1) lumen volume (LV), (2) stent volume (SV), (3) vessel volume (VV), (4) in-stent neointimal volume (ISV) calculated as SV-LV, and (5) percent in-stent neointimal volume (%ISV) calculated as (SV-LV/SV)*100.
Results: Preprocedural volume measurements were similar. At postintervention, both groups achieved a similar SV (140.0 ± 52.7mm^3 vs. 135.2 ± 30.7mm^3, DCA plus stent vs. stent alone). However, the follow-up ISV and %ISV were significantly smaller in the DCA plus stent group than in the stent alone group (19.6 ± 12.2mm^3 vs. 44.6 ± 29.5mm^3; p=0.00040)(15.3 ± 10.6%vs. 31.5 ± 17.7%; p=0.00040), respectively. Consequently, the DCA plus stent group showed the significantly greater follow-up LV (121.0 ± 51.5mm^3 vs. 91.5 ± 26.7mm^3; p=0.016).
Conclusions: Volumetric IVUS analysis demonstrates that plaque removal with DCA before stenting inhibits in-stent neointimal proliferation.

785 Detection of severe left anterior descending coronary artery stenosis by transthoracic Doppler echocardiography and venous adenosine infusion

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Background: Severe left anterior descending coronary artery (LAD) stenosis carries a high risk of acute coronary events, but nevertheless it cannot be reliably predicted by symptoms or standard noninvasive tools. Experimental work shows that coronary flow reserve (CFR) is damped (<1) in severe stenosis.
Aim of this study was to detect severe (>90%) LAD stenosis by transthoracic coronary Doppler ultrasound, an emerging method to noninvasively measure CFR as the ratio between hyperemic and basal coronary flow.
Methods: LAD peak diastolic flow velocity was recorded by transthoracic Doppler echocardiography at baseline and during 90 sec venous adenosine infusion (140 mcg/kg/min), and CFR was measured in 314 subjects, stable and without previous anterior myocardial infarction, 3.7±2 days before coronary angiography. According to angiography, patients were divided into: Group 1 (non-significant, 0-69% LAD stenosis); Group 2 (significant, 70-89% LAD stenosis), and Group 3 (severe, 90-99% LAD stenosis).
Results: Adequate Doppler spectra were obtained in 308/314 (98%) subjects. CFR was 2.86±0.65 in Group 1 (N=197), 1.76±0.52 in Group 2 (N=61), and 0.72±0.17 in Group 3 (N=50), respectively (p<0.001 between groups). A CFR<1 identified severe LAD stenosis with a sensitivity, specificity and positive predictive accuracy of 92%, 98% and 97%, respectively.
Conclusions: Transthoracic Doppler echocardiography allows noninvasive stratification of patients with LAD stenosis. A damped CFR clearly identifies patients with severe stenosis, which may be at high-risk of coronary events.

786 Intracoronary ultrasound of angiographically ambiguous left main coronary artery stenoses. Safety and effect on further clinical decision making

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Purpose: In clinical practice the indications for intracoronary ultrasound (ICUS) have declined in the recent years. ICUS for angiographic uncertain results of the left main coronary artery (LMCA) is one of the more common indications. There is few data in literature about the safety and effect of ICUS on further clinical decision in those cases.
Methods: From September 1996 - July 2001 55 (25%) ICUS of the LMCA out of a total of 221 ICUS were consecutively registered in a large community hospital.
Results: Patients characterization: mean age 61 years, male sex 37 (67%), 40 (73%) stable angina pectoris and 15 (27%) unstable angina pectoris, known coronary artery disease 20 (36%), history of coronary artery bypass grafting (CABG) 10 (18%), history of coronary angioplasty 19 (35%). ICUS of the LMCA was performed due to 39 (71%) angiographically ambiguous ostial lesions (group 1) and 16 (29%) presumed distal lesions (group 2). ICUS was feasable in 100%. There were no major ICUS-related complications: 4 (7%) patients had asymptomatic, 1 (2%) had temporary symptomatic coronary spasms. The ICUS-results of both groups are shown in table 1. Only due to ICUS findings 12 (22%) CABG were performed because of severe LMCA-stenoses, 17 (31%) presumed high-graded LMCA-stenoses could be excluded, so that an intervention was unnecessary, ICUS confirmed 26 (47%) angiographically presumed results and therefore did not change the further clinical decision making.

LMCA-stenosis graded by ICUS:	Group 1 (n=39/55)	Group 2 (n=16/55)
Mild (< 40%)	8 (21%)	13 (81%)
Moderate (40-70%)	19 (49%)	3 (19%)
Severe (>70%)	12 (30%)	0 (0%)

Conclusions: In the daily clinical routine ICUS of the LMCA in cases with ambiguous angiographic results is feasable and save, if performed by a skilled examiner. With 25% of all performed ICUS it has become an important indication. ICUS was diagnostic in 100% and in more than 50% of cases ICUS-diagnosis made the further clinical decision.

787 Importance and role of multiplane transoesophageal echocardiography in diagnosis of anomalous origin of coronary arteries

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Background: Nowadays X-ray cineangiography has been the imaging modality of choice for coronary arteries assessment. However, this technique does not reliably delineate the proximal course of anomalous coronary arteries (ACA) in relation to the aorta or pulmonary trunk. This information is often critical to the management of these patients (pts). This study describes the importance of integration of data obtained from digital coronary angiography with Multiplane Transesophageal Echocardiography (MTE) in evaluating the anomalous origin and course of coronary arteries and their haemodynamic significance.
Methods: ACA were detected by coronary angiography (from November 1998 to September 2001) in 19 pts (12 males, 56.8±8.3 years old). All pts underwent MTE to evaluate the relationship of the ACA with Aorta and Pulmonary Artery. In all cases a Stress/Rest 99mTc Sestamibi myocardial perfusion single photon emission tomography (SPECT) was performed.
Results: The MTE showed a course of the ACA between the aorta and the pulmonary trunk in the 7 pts with right coronary artery originating form the left sinus of Valsalva and in the 2 pts with single coronary artery originating form the right sinus of Valsalva; all these 9 pts had a perfusion defect at SPECT. In the other 10 pts (6 with circumflex coronary artery form the right sinus of Valsalva and 4 pts with a high right coronary artery) the MTE showed a course of the ACA anterior or posterior to the aorta and the pulmonary trunk and no perfusion defect was detected at SPECT.
Conclusion: MTE is a non-invasive and accurate technique for detecting anomalous origin of coronary arteries. In this series, MTE correctly identified every anomalous course; an anomalous course between Aorta and Pulmonary artery was associated with a myocardial perfusion defect detected by SPECT. Evaluation of the haemodynamic importance of the ACA can be useful in programming corrective surgery.

788 Estimation of coronary artery stenosis with retrospective electrocardiogram-gated multislice CT

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We estimated the accuracy of multislice CT (MSCT) in the detection and quantification of significant (>50%) coronary artery stenosis, in comparison with coronary angiography.
Material and method: Between January and June 2001, 90 patients (43 women and 47 men, mean age 67 SD 14 years) with stable effort angina were included to prospective blinded study. All patients underwent MSCT and digital CA in consecutive five days. MSCT were performed on a MSCT scanner Somatom Plus 4 Volume Zoom (Siemens, Erlangen, Germany). CA were carried out by angiographer Coroscope (Siemens, Germany) (QCA). Every patient was medicated with beta blocker to reduce heart rate below 75 bpm. 2 ml/kg of non-ionic contrast was administered (4 ml/s). Acquired images were sent to a workstations and reconstructed and post- processed (Wizzard Siemens, Silicon Virtuoso Siemnes). The stenosis quantification with MSCT was done in each coronary segment by 1) 2 - reconstruction (curved MPR, 5 mm thin MIP) and 2) 3-D reconstruction. 559 coronary artery segments were assessed: 155 of right coronary artery (segments 1,2), 90 of left main (5), 165 of left anterior descendent artery (6,7), 149 of circumflex artery (11,12).
Statistical analysis: the 95% confidence intervals (CI) for the proportions were calculated with use of the exact binomial method.
Results: 161 (28.8%) segments out 559 had significant stenosis (> 50%) as determined by CA. Mean heart rate during MSCT examination was 59 SD 18 bpm.
The total true negative results were 323, true positive - 135, false negative - 26, false positive 75. Sensitivity and specificity were 83.8% (CI 76%- 84%) and 81.1% (CI 77% - 85%) respectively Positive predictive value was 64% (59% - 67%), negative predictive value was 92.5% (CI 81% - 94%)
Conclusion: MSCT is a promising instrument in non-invasive detection of coronary stenosisin a proximal and medial part of the arteries. This method may be an interesting alternative in patients with high-risc angiography.

NEW PATHWAYS OF ENDOTHELIAL CELL MODULATION

789 The arginase pathway in human endothelial cells: characterisation and role in pathophysiologic conditions

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Arginase is a nitric oxide synthase-alternative breakdown pathway for L-arginine, leading to biosynthesis of urea and L-ornithine instead of nitric oxide. The arginase pathway is inducible by inflammatory molecules - such as cytokines and bacterial endotoxin - in different cell types (e.g. macrophages, smooth muscle cells).
Aim: To test whether the arginase pathway is present in human endothelium and susceptible of modulation by inflammatory molecules.
Methods: We have: (1) characterised the arginase pathway in terms of activity, isoform type and gene expression in a primary human cell line (HUVEC), (2) determined the effects of inflammatory molecules on the arginase pathway, (3) investigated the signal-transduction involved and (4) evaluated the functional implications of arginase pathway in cell proliferation.
Results: HUVEC showed a baseline arginase activity due to gene and protein expression of the mitochondrial arginase isoform (A-II). After addition of a cytomix (tumour necrosis factor-alpha + E. Coli lipopolysaccharides), arginase activity time-dependently increased reaching a peak after 48 hours. Such increase was not consistent with an increase in A-II protein expression or with A-I induction. Immunoprecipitation experiments showed that the cytomix increased the phosphorylation of A-II tyrosine residues. In addition, urea measurements with genistein (a tyrosine kinase inhibitor) and sodium orthovanadate (a tyrosine phosphatase inhibitor) confirmed a tyrosine phosphorylation-mediated control of arginase activity. Cell cycle analysis and nuclear factor Ki-67 immunostaining revealed that baseline arginase activity is fundamental for HUVEC proliferation. Cytomix, although inducing arginase activity, caused cell-cycle arrest, suggesting that other intracellular pathways may play a major role in the control of cell proliferation during inflammatory conditions.
Conclusions: The arginase pathway is present in HUVEC where it contributes to cell cycle regulation. The arginase activity is positively modulated by cytomix via a post-transductional mechanism.

790 Flow-induced haptoglobin expression is partly regulated via a NO-mediated pathway

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Background: Flow-induced remodeling is an attempt to restore local shear stress. Nitric oxide (NO) is an important mediator of this process and regulates cell proliferation, migration and gene expression. Previously, we demonstrated that arterial haptoglobin expression increased early after flow-induced remodeling. Haptoglobin was found to play an important role in cell migration during tissue restructuring. Haptoglobin expression is mainly regulated through interleukin-6 which expression is influenced by shear stress and NO. In the present study, we hypothesized that flow-induced haptoglobin expression depends on the upregulation of IL-6 via a NO-mediated pathway.
Methods: In 14 New Zealand White rabbits, the right carotid artery was completely ligated which resulted in a flow increase in the contralateral left carotid artery. Animals were terminated after 1 day. Rabbits received either L-NAME (a nonspecific NO synthase inhibitor) starting 5 days before intervention (L-NAME treated rabbits, n=7) or served as control group (control rabbits, n=7). The carotid arteries of 6 additional unoperated untreated rabbits were used for baseline values. Quantitative PCR and western blotting was performed to study haptoglobin and interleukin-6 (IL-6) expression.
Results: One day after ligation, a significant increase of haptoglobin mRNA (30-fold, $p=0.003$) and protein (1.6-fold, $p<0.05$) was observed in both carotid arteries of control rabbits. Compared to baseline values, haptoglobin mRNA (12-fold, $p=0.004$) and protein (1.4 fold, $p<0.05$) was also significantly increased in both carotid arteries of L-NAME treated rabbits. Absolute haptoglobin mRNA levels, however, were significantly lower compared to control rabbits (3-fold, $p<0.04$). IL-6 mRNA levels significantly increased in both carotid arteries of the control rabbits compared to baseline values (4-fold, $p<0.03$). No changes in IL-6 expression levels were observed in the carotid arteries of L-NAME treated rabbits.
Conclusions: Haptoglobin expression after flow changes is partly regulated via IL-6 in a NO-mediated pathway.

791 Calpain prevents p53 dependent apoptosis in vascular smooth muscle cells exposed to mechanical stretch

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Background: Increased mechanic forces as ocuring in severe hypertension or venous bypass grafts cause rapid onset of apoptosis of vascular smooth muscle cells (VSMC), initiating chronic remodeling processes. Although involvment of the protease calpain for cell migration, proliferation, and apoptosis has been suggested, its role in early triggers of apoptosis after mechanic stress remains obscure. We hypothesized that calpain influences apoptosis induced by mechanic stress of VSMC in vitro.

Methods and results: Quiescent, mitogen-free rat VSMC were subjected to cyclic-stretch for up to 24 h (0,5 Hz at 120% resting length). 15 min of stretch increrased calpain activity 2.4±0.4 fold (*compared to unstretched cells, n=6, $p<0.001$) as measured by cleavage of the fluorigenic calpain substrate SLLVT-AMC. This rapid activation was dependent on calcium influx since inhibition of stretch-activated calcium channels with gadolinium (Gd3) or prevention of intracellular calcium release with TMB8 significantly reduced calpain activity (1.3±0.2 and 1.4±0.2 fold* respectively). Stretch resulted in a significant increase of apoptotic nuclei from 3±1% to 8±2% as measured by dUTP-biotin nick end labeling (TUNEL) after 24 h of stretch. The pharmacologic calpain inhibitors PD150606 or calpeptin dramatically augmented stretch-induced apoptosis rate to 35±4% and 30±6% of cells respectively. Immunoblot analysis of homogenates 24 h after stretch revealed that the stretch-induced increase in p53 level as well as p21 expression and Bax/bcl-2 ratio was further augmented in cells treated with calpain inhibitors.

Conclusion: Calpain is rapidly activated in VSMC exposed to cyclic stretch in a calcium dependent manner, regulating p53 expression levels and thereby preventing p53 dependent apoptosis. Targeting calpain may represent a novel strategy to influence vascular remodeling induced by mechanic overload.

792 Gene transfer of isolated beta-integrin cytoplasmic domains causes endothelial cell apoptosis via caspase activation in vivo

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Integrins are a class of adhesion receptors that are necessary for vascular cell development and migration, as well as extracellular matrix assembly. The aim of the present study was to study the role of integrin in endothelial cell (EC) adhesion and survival.

Methods: We have constructed a recombinant adenovirus (Ad) vector expressing a chimeric protein consisting of the cytoplasmic and transmembrane domains of the integrin beta-1-subunit (CH1) fused to the extracellular L3T4 domain. An adenovirus vector expressing a chimeric protein consisting of the transmembrane but not the cytoplasmic beta-1-integrin domain fused to the extracellular L3T4 domain (CH2) was used as a control. These vectors were tested on EC monolayers (HUVEC) in vitro and in rat carotid arteries in vivo. Rat arteries were explanted at 8, 24, and 48 hours, and 6 days after gene transfer with Ad-CH1and Ad-CH2 (n = 2 per vector and time point). Transduced EC were detected by immunohistochemical double-labeling with antibodies to L3T4 and the von Willebrand factor (n = 20 sections/vessel). Apoptosis was detected by TUNEL and by immunohistochemistry using a monoclonal antibody that recognizes activated caspase-3.

Results: Ad-CH1caused EC detachment from several extracellular matrix substrates and apoptosis in a dose-dependent manner in vitro. Ad-CH1 and Ad-CH2 transduced ~20% of EC in rat arteries in vivo. CH1 expression was observed at 6 and 24 hours but not at later time points, whereas CH2 expression was observed at all time points. A large proportion of CH1-transduced EC lost their normal flattened morphology, rounded up and detached from the vessel wall. In contrast, CH2 transduced EC retained their flattened morphology. Positive TUNEL and caspase-3 activation was detected in EC transduced with CH1 but not CH2 constructs.

Conclusions: These findings provide first evidence that gene transfer of dominant-negative beta-integrin constructs induces endothelial cell detachment and apoptosis via caspase activation in vivo. Therefore, these results demonstrate that beta-integrins are essential for arterial endothelial cell adhesion and survival. Potential applications of this approach to pathophysiological processes involving integrin-dependent cell adhesion and migration may include dysruption of vessel integrity in tumor angiogenesis.

793 Amelioration of vasculopathy in diabetic db/db mice by the NHE-1 inhibitor cariporide

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Diabetic vasculopathy is characterized by both vascular smooth muscle and endothelial dysfunction. In the present study we tested the hypothesis that chronic treatment with the NHE-1 inhibitor cariporide- mesylate improves endothelial function in a type II diabetic mouse model. Using standard organ bath techniques, we measured phenylephrine (500 nM)-mediated contraction as well as endothelium dependent (acetylcholine, 100 nM to 10 μM) and endothelium independent (sodium nitroprusside, 10 nM to 10 μM) relaxation in aortic rings from 37 week old male mice in three groups: a) lean, non-diabetic db/- mice (LEAN, n=5); b) obese, diabetic db/db mice (OB, n=5), and c) obese, diabetic db/db mice pre-treated with cariporide, 0.6% (v/v) in chow for 27 weeks (OB+CARI, n=6). Maximum tension in response to phenylephrine (500 nM) was increased in rings from OB (462 ± 54 mg) than from LEAN (326 ± 35 mg, $p<0.05$ vs. OB) and OB+CARI (342 ± 25 mg, $p<0.05$ vs. OB). The maximal endothelium dependent relaxation induced by acetylcholine (10 μM) was depressed in OB vs. LEAN (62 ± 6% vs. 100 ± 2%, $p<0.05$). Pre-treatment with cariporide ameliorated endothelium dependent relaxation (OB+CARI: 105 ± 13%, $p<0.05$ vs. OB). Endothelium independent aortic relaxation induced by sodium nitroprusside was not different between the three groups. In conclusion, diabetic vasculopathy in db/db mice is characterized by both smooth muscle hypercontractility and impaired endothelium dependent relaxation. Chronic treatment with the NHE-1 inhibitor cariporide ameliorates diabetic vasculopathy and improves endothelial function in this type II diabetes animal model.

794 Lessons from a DDAH transgenic mouse: role of ADMA in regulating NOS activity and blood pressure

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Asymmetric dimethylarginine (ADMA) is a competitive inhibitor of nitric oxide synthase (NOS). ADMA is metabolized to citrulline and dimethylamine by dimethylarginine dimethylaminohydrolase (DDAH). We generated a transgenic mouse that overexpresses DDAH using human DDAH I cDNA, a human B-actin promoter and RNA processing signals from SV40, cloned into a pBluescript vector. Purified DNA was used for pronuclear microinjection. DNA from newborn mice was subjected to Southern blot analysis to identify the presence of the transgene. Western blotting confirmed human DDAH expression in all tissues. In all subsequent studies, heterozygous transgenic mice were compared to age, weight and sex matched wildtype controls. The DDAH transgenic mice appear normal at birth, and pathologic studies disclosed no anatomic abnormalities. Biochemical studies revealed that plasma ADMA levels were 50% of normal mice. The reduction in plasma ADMA was associated with a 2-fold increase in tissue NOS activity. This was confirmed by ex-vivo studies of transgenic endothelial cells which manifested an increase in NO production. Tail cuff measurements of blood pressure in conscious animals demonstrated a 6.8 mmHg reduction in systolic blood pressure in comparison to wildtype controls ($P<0.05$).

In conclusion, DDAH overexpression caused a decline in plasma ADMA levels which was associated with increased tissue and endothelial NO synthesis. The increase in NO synthesis was associated with a reduction in blood pressure. This is the strongest evidence to date that ADMA is an important regulator of NO synthesis, and also indicates that changes in DDAH activity may have physiologically and clinically relevant effects

MOLECULAR STUDIES IN ATHEROSCLEROSIS

795 Low density lipoprotein receptor-related protein expression, regulation and function in VSMC of normal and atherosclerotic human coronaries

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Background: Low density lipoprotein receptor-related protein (LRP) is expressed in normal vessels and atherosclerotic plaques. LRP expression may increase in rabbit atherosclerotic lesions. We have previously demonstrated that LRP binds and internalizes aggregated-LDL (agLDL) formed by interaction with the extracellular matrix proteoglycan versican in human vascular smooth muscle cells (VSMC).
Objectives: To analyze LRP expression, LRP regulation by agLDL and LRP function in VSMC of normal and atherosclerotic human coronaries.
Methods: Human coronary arteries were obtained from excised hearts and LRP expression in normal vessels (n=7) and atherosclerotic plaques (n=5) was analyzed by in situ hybridization and immunohistochemistry. Normal or plaque-derived VSMC (passage 2) were obtained by the explant technique analyzing mRNA and protein levels by semiquantitative RT-PCR and Western blot. Additionally, we analyzed the regulation of LRP expression levels in normal and plaque-derived VSMC in the presence of increasing concentrations of agLDL (from 50 mg/ml to 200 mg/ml). LRP function was analyzed by measuring the cholesteryl ester (CE) content of VSMC by TLC after 18 hours incubation with agLDL.
Results: Immunohistochemical analysis shows that LRP expression is increased in human atherosclerotic plaque VSMC. Plaque-derived VSMC express higher levels of LRP protein than normal VSMC (645.4±172 AU vs 332±95 AU; $p<0.05$). In agreement, plaque-derived VSMC accumulate higher intracellular CE levels than normal VSMC when exposed to agLDL (200 mg/ml) (110±15 mgCE/mg prot. vs 70±7.5 mgCE/mg prot; $p<0.05$). AgLDL induces higher LRP expression in plaque-derived VSMC (2.3-fold) than in normal VSMC (1.2-fold).
Conclusions: These results indicate that plaque-derived VSMC have higher LRP expression and capacity to internalize agLDL than normal VSMC. The LRP up-regulation in plaque-derived VSMC induced by agLDL suggests that LRP expression can be readily induced by aggregated intimal LDL and that the high LRP expression observed in atherosclerotic plaque VSMC might be conditioned by the enriched lipidic environment. LRP mediated internalization of intimal LDL by VSMC might be one of the main mechanisms contributing to atherosclerotic plaque progression

796 Molecular cloning and characterization of the human KIS gene promoter – a regulator of vascular smooth muscle cell proliferation

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Vascular smooth muscle cell proliferation plays a major role in atherosclerosis and restenosis. The cyclin-dependant kinase inhibitor p27Kip1 arrests cell-cycle progression by inhibiting the phosphorylation of CDKs and the retinoblastoma gene family products. We have previously shown that p27Kip1 negatively regulates vascular smooth muscle proliferation. Using a yeast-2-hybrid screen and the C-terminal portion of p27Kip1 as bait, we have identified a novel kinase (hKIS) that phosphorylates p27Kip1 on serine 10, leading to degradation of p27Kip1 and cell-cycle progression. To investigate the mechanism of transcriptional hKIS gene expression, we isolated the genomic DNA fragment of the 5' flanking region of the hKIS gene and characterized its promoter region. The transcription initiation start-site was mapped by RNase protection assays to approximately 170 bp upstream of the translational start-site. Transient transfection assays using fusion reporters containing progressively truncated hKIS promoter fragments showed that a region of 250 bp upstream of the translational start site is sufficient for maximal transcription activity and is highly homologous to the mouse KIS promoter sequence. Deletion analyses have revealed several putative transcription-factor binding sites that are likely involved in the regulation of hKIS gene expression. In particular, deletion of consensus sequences for Sp-1, Ets-1 and GATA-2 showed a marked reduction in basal promoter activity suggesting that they may regulate the basal expression of hKIS. Thus, hKIS is transcriptionally regulated and potential inhibitors of hKIS gene expression are being defined to modify its expression. Such studies will be useful in expanding our understanding of the important roles that hKIS and p27Kip1 play in regulating vascular smooth muscle proliferation.

797 Cell-cell contact via cadherin-catenin complexes is essential for vascular smooth muscle cell survival

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Death of vascular smooth muscle cells (VSMCs) via apoptosis causes subsequent thinning of the fibrous cap and contributes to the propensity for plaque rupture. The cadherins and their adaptor proteins, the catenins, mediate calcium-dependent cell-cell contacts that maintain cell survival in some cell types, but little is known of their role in VSMCs. In this study cell-cell contact, without cell-matrix contact, was permitted by culturing VSMCs at high density on agarose-coated plates. The addition of 2mM EGTA chelated extracellular calcium and inhibited cell-cell contact. VSMC death assessed by trypan blue staining, was significantly higher in VSMCs grown without cell-cell contacts (EGTA-treated) for 24 hours, than in VSMCs grown at high density where cell-cell contacts formed, (57±16% v 20±9%: n=6; $p<0.05$). In situ end labeling and hoescht and propidium iodide staining confirmed trypan blue staining results. Expression of N- and T-cadherin proteins was significantly greater in VSMCs with cell-cell contact than in VSMCs in the absence of cell-cell contact. In addition, cleavage of the cadherin adaptor protein, beta-catenin was observed in VSMCs in the absence of cell-cell contact. To induce apoptosis VSMCs were cultured with a bcl-2 antagonist (HA-14 at 50μM). After 6 hours culture only a few cells showed apoptotic characteristics whilst 100% did at 16 hours. The level of N-cadherin protein expression was reduced by 72±21% at 6 hours (prior to appearance of apoptotic VSMCs) and by 100±0% at 16 hours, suggesting that this loss is not just a consequence of apoptosis. However, although T-cadherin protein expression was abolished at 16 hours, it was unaffected at 6 hours. This study indicates that cell-to-cell adhesion mediated by cadherins, particularly N-cadherin, acts as a survival signal for VSMCs. We suggest maintenance of cell-cell contacts via cadherins is a viable strategy for reducing VSMC apoptosis and plaque rupture.

798 Statins inhibit cyclooxygenase-2 protein and activity in human endothelial cells – Possible contribution to plaque stability

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The 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) are currently being investigated for cholesterol-independent properties, among which anti-inflammatory effects. Cyclooxygenase(COX)-2 expression within atherosclerotic plaques has been linked to plaque instabilization through COX-2-dependent expression of matrix metalloproteinases. Accordingly, statins reduce basal and stimulated metalloproteinase expression by macrophages. Since vascular endothelium plays a crucial roie in the development of atherosclerotic lesions, we investigated whether statins modulate endothelial COX-2.
Methods: Simvastatin and atorvastatin, in vitro activated by alkaline hydrolysis, were incubated with human umbilical vein endothelial cells (HUVEC) for 6 h, followed by stimulation with tumor necrosis factor (TNF), lipopolysaccharide (LPS) or phorbol myristate acetate (PMA) for further 12 h. After this time, COX-2 activity and protein were assessed by a radioimmunoassay for 6-keto-PGF1alpha (the stable hydrolytic metabolite of prostacyclin) and Western analysis, respectively.
Results: At 0.1-10 μmol/L, and in the absence of any toxicity, both simvastatin and atorvastatin reduced COX-2 expression and prostacyclin production without any effect on COX-I expression. Results for COX-2 protein expression at Western blot densitometry are shown in the Table.
The effect of both statins on COX-2 protein expression was totally reversed by the addition of 200 μmol/L mevalonate, indicating the requirement of a prenylated intermediate in the signal transduction pathway leading to COX-2 expression. 6-keto-PGF1alpha production was (pg/1000 cells) 0.22±0.01 in control conditions, 4.88±1.72 after PMA 6.3 ng/mL, 2.60±1.34 after PMA in the presence of simvastatin ($P<0.01$ vs PMA), and 4.42±1.36 after PMA with simvastatin + mevalonate (P = N.S. vs PMA).

The effect of statins on COX-2 protein

Stimulus	Simvastatin 1 μmol/L (% of stimulated control)	Atorvastatin 1 μmol/L (% of stimulated control)
PMA 6.3 ng/mL	15 ± 4**	38 ± 10**
LPS 1 microg/mL	67 ± 22*	79 ± 25*
TNF alpha 10 ng/mL	13 ± 4**	34 ± 9**

* = $P<0.05$; ** = $P<0.01$ vs stimulated control without statins

Conclusions: Statins reduce the induced expression and activity of COX-2 in human vascular endothelial cells. This effect may contribute to clinical benefits of statins, independent of cholesterol-lowering.

799 Nicotine efficiently stimulates T cell immune responses via dendritic cells and monocytes: potential role for atherosclerotic lesions progression

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Atherosclerosis is a chronic inflammatory disease. Antigen presenting cells such as monocytes (MC) and dendritic cells (DC) are able to stimulate T cell proliferation in atherosclerotic lesions, contributing to formation and/or destabilization of atherosclerotic lesions. Our previous data demonstrate that nicotine stimulated progression of advanced atherosclerotic lesions. Accordingly, we investigated whether nicotine stimulates antigen presenting cells and their T cell stimulatory capacity. We used human monocyte-derived DCs and their monocytic precursors as antigen presenting cells. Nicotine dose-dependently (10-10to 10-6 M) induced expression of nicotinic acetylcholine receptors (nAChR), co-stimulatory molecules such as CD86, MHC class II molecules such as HLA-DR, and adhesion molecules such as CD54. Moreover, nicotine induced the secretion of the pro-inflammatory TH1 cytokine IL-12 in DCs and MCs (5.0-fold and 7.0-fold increase over control ($p < 0.01$), respectively). Nicotine-induced expression of surface molecules and IL-12 production was inhibited by the general nAChR antagonist mecamylamine and a7-nAChR antagonist a-bungarotoxin, respectively. To elucidate the functional relevance of nicotine-stimulated antigen presenting cells, we used mixed lymphocyte reactions (MLRs) where T cell activation was measured by induction of the T cell-specific cytokine IL-2. Nicotine-treated DCs and MCs showed a strong increase in IL-2 production by allogeneic T cells (4.2-fold and 2.7-fold induction over control ($p < 0.01$), respectively).
In conclusion, nicotine exerts a potent stimulatory effect on T cell stimulation via dentritic and monocytic cells. The activation of these immune competent cells may significantly contribute to the nicotine-promoted progression of atherosclerotic lesions.

800 Proteasome inhibition leads to NF-kB independent interleukin-8 transactivation in human endothelial cells through induction of JNK-kinase

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Interleukin-8 (IL-8) is an important mediator of leukocyte trafficking and activation, participating in tumor angiogenesis, inflammatory processes and coronary atherosclerosis. Under flow conditions IL-8 triggers in conjunction with MCP-1 the firm adhesion of monocytes to the vascular endothelium. While previous studies have suggested the requirement of NF-kB for IL-8 secretion by endothelial cells, we investigated the possibility of IL-8 transactivation under conditions of NF-kB suppression.
Methods and Results: Inhibition of the proteasome by MG-132 or lactacystin completely blocked TNF-induced IkBalpha-degradation as well as NF-kB activity in human arterial endothelial cells. Surprisingly, basal secretion of IL-8 protein was 8 to 10-fold induced by proteasome inhibitors while MCP-1 expression was, as expected, completely downregulated. IL-8 was upregulated at the transcriptional level, and promoter studies prooved a more than 9-fold induction of AP-1 actvity to be the cause of increased IL-8 transcription. Mutation of the AP-1 binding site in an IL-8 promoter construct completely abrogated this effect, while mutation of the NF-kB motif did not influence IL-8 transactivation by proteasome inhibitors. DNA binding assays found a 7- to 8-fold induction of phosphorylated c-jun and hence JNK kinase activity under MG-132 treatment. Induction of JNK kinase appeared independent of the cell type, even in tumor cell lines not responding to proteasome inhibitors. Since neither inactivation of p53 in wild-type p53 cells nor reintroduction of functional p53 into p53-/- cells affected MG-132-inducible IL-8 secretion, a direct influence of p53 on IL-8 regulation could be excluded.
Conclusion: These results show that proteasome inhibitors can not only lead to functional AP-1 induction by enhanced c-jun phosphorylation, but also transactivate the IL-8 gene in human endothelial cells despite complete suppression of NF-kB activity.

CLINICAL CORRELATES IN ALTEROSCLEROSIS

801 Is there a reverse relation between serum paraoxanase activity and the angiographic extent of coronary atherosclerosis

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Background: HDL has been shown to prevent the oxidation of low-density LDL. The antioxidant activity of HDL is believed to reside in its enzymes, particularly paraoxanase (PON). PON has also been reported to be decreased patients with atherosclerosis. But, it is not investigated relation between serum PON activity and the extent of coronary atherosclerosis. This study was conducted to investigate possible relation between serum PON level and extent of coronary atherosclerosis in patients with unstable angina pectoris (UAP) and non-Q-wave acute myocardial infarction (NQAMI).
Methods: Consecutive 85 patients (68 male, mean age: 56.4 ± 9.3 years) with UAP and NQAMI (group I) and age-matched 40 healthy subjects (33 male, mean age: 55.7 ± 8.1 years) as control group (group II) were included in this prospective study. Coronary angiography was performed to all patients, and films from coronary angiography were viewed and scored using Sullivan's method to assess extent of coronary atherostherosis. Serum PON activity was measured by enzymatic activity.
Results: The serum PON activities were significantly lower in group I than in group II (respectively 64.3 ± 10.1U/ml, 95.6 ± 24.5U/ml; $p<0.0001$). There was a significant negative correlation between serum PON activities and Sullivan's extent score in patients with UAP and NQAMI (r: -0.82; $p<0.001$).
Conclusion: 1. Serum PON activity, which is prevent the oxidation of LDL, was significantly lower in patients with UAP and NQAMI. 2. There was significantly correlation between serum PON activity and the extent of angiographically determined coronary atherosclerosis.

802 Serum interleukin-18 is a strong and independent predictor of future cardiovascular events

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Introduction: Interleukin (IL) 18 is a pleitropic cytokine acting in acquired and innate immunity. Increased expression of IL-18 could be demonstrated in atherosclerotic, esp. vulnerable plaques. In light of its central role in the inflammatory cascade we evaluated the association of serum IL-18 with future cardiovascular events in a large cohort of patients (pts) with coronary artery disease (CAD).
Methods: In 1533 pts with documented CAD IL-18 [pg/ml], high sensitive C-reactive protein (hs-CRP) [mg/dl], fibrinogen [mg/dl], and white-cell count [/nl] count were determined. 1525 (99.6%) had a follow up (f/u) after a mean of 3.9 (maximum 5.2) years.
Results: During f/u 128 pts died because of cardiac reasons. Serum levels of IL-18 were significantly higher in pts suffering from future cardiovascular death (69.4 versus 58.8 pg/ml, $p<0.0001$). Increasing quartiles of IL-18 were associated with a 1.5 fold (95%CI 1.2 to 1.8; $P<0.0001$) increase in risk. This relationship was not weakend by fully adjustment for most potential confounders (see legend of table) as well as adjustment for other inflammatory markers like hs-CRP, fibrinogen, or white-cell count. By contrast, the latter markers lost its prediction after controlling for IL-18.

	Q1	Q2	Q3	Q4
range [pg/ml]	<45.2	45.2 - 60.3	>60.3 - 78.8	>78.8
% CV mortality	3.4	5.2	11.4	10.5
HRR	1	1.8	2.7	3.1
95% CI	–	0.8 - 4.4	1.2 - 6.1	1.4 - 7.2
P value multiv.	–	0.2	0.02	0.006

Fully adjusted model for age, sex, bmi, classical risk factors, clinical and therapeutic features including acute coronary syndrom, extent of vessel disease, history of MI, betablocker and statin medication, interventional therapy, and ejection fraction; HRR denotes Hazard Risk Ratio; cv cardiovascular.

Conclusion: We could demonstrate for the first time the strong and independent association between IL-18 serum concentration and future cardiovascular events. These results strengthens the role of IL-18 in atherogenesis and plaque destabilization and might offer a tool for a more accurate risk prediction.

803 Influences of age and gender on results of brachial-ankle pulse wave velocity measurement – a survey of 8607 normotensive health subjects

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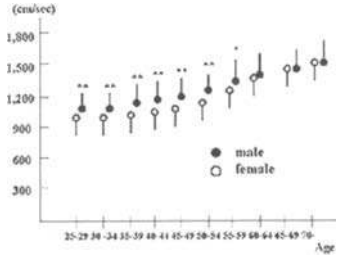
The present study was conducted to evaluate the influences of age and gender on the results of noninvasive brachial-ankle pulse wave velocity (baPWV) measurement in apparently healthy subjects. A total of 8,607 healthy subjects (5,144 males and 3,463 females; range: 25 to 87 years) were studied, in whom coronary risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking) had been excluded. baPWV was measured using volume rendering method. In all subjects, results of baPWV were analyzed chronologically in 5-year age intervals (from 25 to over 70 years). The baPWV was lower in females than in males until age 60, and became similar in both genders over age 60. Step-wise multiple regression analysis of the relationship between baPWV and other clinical variables including pulse pressure and mean blood pressure demonstrated that age is an independent variable for baPWV in both genders (male: beta = 0.25 R-square = 0.33, female beta = 0.39 R-square = 0.53, $p<0.01$). In this analysis, not only the value of R-square but also the coefficient of the effect of age on baPWV are larger in females than in males. In the estimation of the regression curve, the relationship between age and baPWV demonstrated a quadratic curve in both genders {Male: baPWV = 0.19 x age2 - 11.01 x age + 1327.61 (r =0.24, $p<0.01$), Female: baPWV = 0.20 x age2 - 8.22 x age + 1076.33 (r =0.43, $p<0.01$)}.



Thus, aging influences baPWV, and its effect is more prominent in female. In this respect, menopause seems to be the crucial phenomenon to explain the augmented increase in arterial stiffness with aging in females.

804 Determinants of matrix metalloproteinases plasma concentration and activity in premature coronary atherosclerosis

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Background: matrix metalloproteinases (MMPs) are thought to participate in the pathogenesis of coronary artery disease (CAD), particularly in the occurrence of acute coronary syndromes (ACS). Little is known on determinants of MMPs concentration and activity in vivo.
Methods: we studied 80 young (<55 years) male patients with either myocardial infarction (MI) or angina (A) with angiographic evidence of CAD and 40 healthy male controls of similar age. Patients were subdivided into three groups as follows: 1)20 consecutive ST elevation acute MI (STEMI), 2)29 consecutive unstable A (UA) or non-STEMI (UA/NSTEMI group), 3)31 consecutive previous MI and/or stable A (SA) (stable CAD group; SCAD). We determine plasma concentration of gelatinase A (MMP-2), stromelysin-1 (MMP-3), gelatinase B (MMP-9) and specific tissue inhibitors of MMPs, such as TIMP-1 and TIMP-2. MMP-2 and MMP-9 total plasma activity was also measured along with serum concentration of C-reactive protein (CRP), haptoglobin (HPT), alpha 2-macroglobulin and tumor necrosis factor-alpha.
Results: MMP-9 concentration, but not total activity, was higher in ACS patients than in controls ($p<0.001$). Remarkably, neither MMP-9 concentration or total activity correlated with inflammation markers. MMP-2 total activity, but not MMP-2 concentration, was lower both in the whole population ($p=0.002$) and in ACS patients ($p<0.001$) compared to controls. MMP-2 total activity, but not concentration, correlated inversely with HPT ($r=-0.195$, $p=0.032$), blood glucose ($r=-0.250$, $p=0.006$) and total cholesterol levels ($r=-0.214$, $p=0.021$). MMP-3 concentration was similar in patients and controls. As regards TIMPs, the concentration of TIMP-1 was higher both in the overall population ($p<0.001$) and in ACS patients ($p=0.018$) with respect to controls. By contrast, TIMP-2 was lower in all groups of patients ($p<0.001$). TIMP-1 strongly correlated with blood glucose ($r=0.711$, $p<0.001$) and both CRP (0.594,$p<0.001$) and HPT ($r=0.276$,$p=0.005$). Among inflammation markers, only CRP and HPT were significantly higher in patients than in controls (both $p<0.001$).
Conclusions: in patients with premature CAD MMP-9 and TIMP-1 concentrations are increased and TIMP-2 concentration and MMP-2 total activity are decreased. The correlation of MMP and TIMP plasma levels with inflammation markers was restricted to TIMP-1 and MMP-2 total activity. These findings suggest that more attention should be focused on how inflammation and metabolic disorders could influence MMPs plasma concentration and activity.

805 Decreased baroreflex sensitivity depends on the atherosclerotic damage of the carotid arteries

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Low baroreflex sensitivity (BRS) in patients after acute myocardial infarction (AMI) has been proven as an independent risk factor of major cardiac events. It may be suspected that the atherosclerotic involvement of the carotid sinus may cause an impairment of the baroreceptors and influence BRS. To the best of our knowlege, this concept has not yet been tested in post AMI patients.
Methods: BRS was calculated from the measurement of the rate-pressure response to intravenous phenylehprine according to the protocol of the ATRAMI Study. Duplex Doppler ultrasonography of the carotid arteries was performed to identify the degree of the atherosclerotic lesions (ASC) in carotid sinus region. Intima-media complex (IMC) thickness was estimated as the mean value of 10 measurements performed 0.5 cm proximal to bifurcation. Advanced atherosclerosis (ASC +) was defined as bilateral concentric lesion involving >90% of the carotid sinus circumference. The involvement of less than 30% of the carotid sinus circumference was defined as non-significant atherosclerotic lesion (ASC -). Left ventricular (LV) systolic performance was estimated using ejection fraction (EF) and wall motion score index (WMSI) (using transthoracic echocardiography).
Results: The study group consisted of 38 patiens after AMI (mean 11.9 days after AMI, age 60.1 ± 12.6, men 68%). Mean IMC thickness was 0.74±0.18 mm. Mean value of BRS was 4.58±0.57 ms/mmHg. Significant negative correlation was found between BRS value and IMC thickness ($r=-0.74$, $p<0.0001$). Patiens with concentric, bilateral ASC more frequently had severely depressed BRS (<3 ms/mmHg) in comparison to the group without advanced ASC of carotid sinus (chi2=11.57, $p<0.001$)(table). No correlation was found between BRS and parameters of LV function - EF and WMSI ($p=0.88$ and $r=-0.03$, $p=0.51$ and $r=0.14$ respectively).

BRS (ms/mmHg)	ASC (+)	ASC (-)
<3	10 (26.3%)	5 (13.2%)
>3	2 (5.3%)	21 (55.2%)

Conclusion: The bilateral atherosclerotic involvement of the carotid arteries influence the BRS in patients after AMI despite the impairment of left ventricular function. The presence of bilateral, concentric atheromatic plaques results in very low BRS most likely due to baroreceptors damage.

Abstract 804 – Table

	STEMI (N=20)	UA/NSTEMI (N=29)	SCAD(N=31)	CTRL(N=40)	p
MMP-2 concentration (mcg/ml)	554.9±164.3	502.4±170.0	584.8±215.4	494.0±178.3	0.160
MMP-2 total activity (absorbance units)	33.0±21.5	33.9±14.9	35.7±15.5	42.4±14.6	0.073
MMP-3 concentration (mcg/ml)	33.6±15.7	25.0±9.0	28.0±13.6	29.6±12.5	0.130
MMP-9 concentration (mcg/ml)	192.4±123.9	141.5±105.2	82.9±50.1	114.3±74.9	0.000
MMP-9 total activity (absorbance units)	34.8±21.2	30.5±17.7	24.6±10.4	29.5±18.9	0.222
TIMP-1 (mcg/ml)	279.9±72.0	277.5±50.0	298.6±43.0	250.0 ±49.5	0.076
TIMP-2 (mcg/ml)	25.3±11.9	26.2±13.1	23.3±7.2	38.9±12.3	0.000
CRP (mg/dl)	3.8±5.7	1.7±3.4	0.7±1.2	0.1±0.2	0.000
HPT (mg/dl)	200.9±87.6	186.7±80.0	165.7±63.1	113.0±42.3	0.000
ALPHA2 -M (mg/dl)	125.0±35.4	135.9±30.9	137.1±36.9	132.7±36.7	0.647
TNF ALPHA (ng/ml)	4.1±2.0	4.6±3.9	2.8±1.4	3.6±2.0	0.250

806 Cardiac calcification as independent predictor of increased mortality in patients with congestive heart failure: 29-month follow-up

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Objectives: Multiple calcium deposits in the mitral annulus, aortic valve or aortic root are considered markers of CAD severity. However, no data are available concering the impact of those findings on mortality and morbidity in pts with CHF in a prospective follow-up study.
Methods: From January 1996 to January 2001 we prospectively studied 523 consecutive pts (223 males, 300 females, mean age 72±10y) admitted to hospital due to congestive heart failure (NYHA II-IV). Univariate and multivariate analyses were performed to test the association between the presence of aortic valve sclerosis (AVS), aortic root calcification (ARC) and mitral annular calcification (MAC) detected by 2D echocardiography, and 29-month mortality and morbidity. Results: The etiology of CHF was CAD in 218 pts (42%), HTN in 385 pts (74%), DM in 238 pts (46%), stroke in 50 pts (10%), dilated CMP in 17 pts (3%) and other in 103 (20%). AVS (1-Calc) was detected in 203 pts (39%), ARC (1-Calc) in 158 pts (30%) and MAC (1-Calc) in 189 pts (36%). AVS+ARC (2-Calc) were detected in 238 pts (46%) and AVS+ARC+MAC (3-Calc) in 311 pts (59%). No calcium deposits (0-Calc) were observed in 212 pts (40%). The mean follow-up was 28.6±16.3 months. Pts with 1-Calc, 2-Calc and 3-Calc were significantly older than those with 0-Calc (p=0.001). During the follow-up 47 (9%) pts of the 0-Calc group died compared to 165 (32%) pts of the 1-Calc,2-Calc and 3-Calc groups (p=0.001) and 8 (1.5%) pts of 0-Calc group suffered a stroke compared to 21 (4%) pts of the 1-Calc, 2-Calc and 3-Calc groups (p=0.01). Using the Kaplan-Meier survival curve model there was a 19% increase of total mortality in the 3-Calc group compared to pts in the 0-Calc group in the 29-month follow-up (log rank 47.3, p=0.001). After adjusted multivariate Cox proportional-hazard analysis, age (OR 1.05, p=0.0001, 95% CI 1.03-1.07), 1-Calc (OR 1.7, p=0.01, 95% CI 1.15-2.56), 2-Calc (OR 1.6, p=0.05, 95% CI 1.03-2.32) and 3-Calc (OR 2.2, p=0.0001, 95% CI 1.40-3.45) were the only independent predictor of increased mortality. Conclusion: Multiple cardiac calcification presents powerful independent predictor of increased mortality when risk factors for CHF are taken into consideration. This finding identifies a subgroup of pts with CHF as having 19% higher risk of mortality, which is independent of all confounding variables.

COST-EFFECTIVENESS OF CARDIOVASCULAR INTERVENTIONS

807 Carvedilol reduces the costs of medical care in severe heart failure: an economic analysis of the COPERNICUS study applied to the United Kingdom

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Aims: To determine the effect of carvedilol on the costs of treatment for severe heart failure (HF), we prospectively collected resource utilisation data (drug therapy, number of hospital admissions, length and type of hospital stay) in all patients randomized into the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study.
Methods: Costs for the treatment for HF within the National Health Service in the UK were applied to the COPERNICUS data. Unit-specific, per diem (hospital bed day) costs were used to calculate expenditures due to hospital admissions. We included costs of the drug, out-patient clinic visits and nursing home care based on estimates derived from prior evaluations of patterns of clinical practice in the UK.
Results: The estimated cost of carvedilol therapy and related ambulatory care (an average of 5.4 out-patient visits per patient for dosage adjustment) for the 1,156 patients assigned to carvedilol was £530,771 (£44.89 per patient/month of follow-up). However, those assigned to carvedilol were hospitalised less often and accumulated fewer and less expensive days of admission. Carvedilol was associated with a 27% reduction in all-cause hospital stay (7,124 versus 9,603 days: P = 0.0005). Consequently, the estimated cost of hospital care was £3.49 million in the carvedilol group compared with £4.24 million for the 1,133 patients in the placebo arm. The cost of post-discharge care (comprising outpatient and general practitioners visits in addition to nursing home care) was also less in the carvedilol than in the placebo group (£479,200 vs £548,300). Overall, the cost per patient treated in the carvedilol group was £3,889 compared to £4,209 in the placebo group. This equated to a cost of £385.98 vs £434.18, respectively, per patient per month of follow-up: an 11.1% reduction in health care costs in favour of carvedilol. In a series of sensitivity analyses it was found that treatment with carvedilol resulted in a reduction of overall treatment expenditure under a wide range of assumptions.
Conclusions: These findings suggest that carvedilol not only increases survival and reduces hospital admissions in patients with severe HF but likely cuts treatment costs in this patient population as well. This economic evaluation further supports the use of carvedilol in the treatment of HF.

808 A specialist nurse-led management programme in an outpatient population with stable congestive heart failure reduces annual health care costs

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Background: A specialist nurse-led management programme reduces readmission rates and health care costs in patients hospitalised with severe congestive heart failure (CHF). It is unclear whether such a strategy in outpatients with stable CHF would have similar benefits. This prospective, randomized, single centre study assesses such a strategy with respect to hospital admission rates and healthcare costs over a one year period.
Methods: 55 patients (mean age 67 years) with stable CHF (NYHA II-IV) who were attending the cardiology clinic were assigned to receive either usual care (n=26) [Control] or a comprehensive nurse-led management programme which involved education on heart failure and self-management, regular review of medication and problems with compliance, and early identification of worsening CHF under the guidance of a consultant cardiologist (n=29) [Intervention]. Telephonic advice was made available to patients in this group throughout the study. All patients were followed up for 12 months. The main outcome measures were hospital admission rate and health care costs during the study period.
Results: Mean baseline characteristics were similar between the two groups including NYHA CHF class (2.7±0.5 vs 2.7±0.6, p=ns) and mean ejection fraction (31±14% vs 33±12%, p=ns). Reduced hospital (46.2% vs 13.8%, p=0.03) and CHF-related admissions (46,2% vs 6.9%, p=0.02) were noted in the intervention group. There was no difference in length of stay (7.3[10.2] days vs 7.5[11.4] days, p=ns). Mean clinic costs were higher in the intervention group (£294(23) vs £363(56), p=0.05). The mean hospital cost per patient were higher in the control group (£1114[542] vs £207[471], p=0.02). The mean overall annual healthcare cost was significantly lower in the intervention group (£570[512] vs £1409[581], p=0.03.

	Control	Intervention	p
All hospital admissions (%)	46.2	13.8	0.03
CHF-related admissions (%)	46.2	6.9	0.02
Mean hospital stay (days)	7.3(10.2)	7.5(11.4)	ns
Mean clinic/telephone costs (£)	294(43)	363(56)	0.05
Mean hosp. cost/patient (£)	1114(542)	207(471)	0.02
Mean total annual healthcare cost (£)	1409(581)	570(512)	0.03

Conclusions: In a population of outpatients with stable CHF, a specialist nurse-led management programme reduces total, and CHF-related, hospital admissions and is cost-effective.

809 Cost-effectiveness of valsartan in patients not receiving angiotensin-converting enzyme inhibitors at baseline

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Background: Val-HeFT was a multinational randomized trial conducted to evaluate the efficacy of the addition of valsartan to optimal pharmacologic therapy in 5,010 patients with NYHA class II-IV heart failure (HF). Subgroup analyses of 366 patients who were not receiving ACE inhibitors at baseline revealed a lower risk of within-trial mortality and morbidity among patients treated with valsartan.
Objective: To estimate the incremental cost-effectiveness of valsartan in patients not receiving concomitant treatment with ACE inhibitors.
Methods: A multinational cost-effectiveness analysis was conducted using data collected throughout the trial on resource utilization and clinical outcomes. An incremental cost-effectiveness ratio (ICER) is the appropriate measure of cost-effectiveness when a therapy is more effective and more costly. When a therapy is more effective and less costly, it is considered a dominant strategy. Direct medical costs were computed using unit costs from all 16 countries particpating in Val-HeFT (converted to 1999 U.S.$). To estimate the incremental difference in effectiveness, the area under the survival curve was calculated for both treatment groups during the trial period, and the difference is interpreted as life-years saved (LYS). Nonparametric bootstrapping was used to evaluate the variability in the joint distribution of costs and survival.
Results: The average period of follow-up was 23 months. Patients treated with valsartan experienced a 33% reduction in mortality, a 56% reduction in the number of HF-related hospitalizations (51 vs 117) and a 24% reduction in the number of all-cause hospitalizations (199 vs 262). Using point estimates of the differences in costs and survival, valsartan was shown to be a dominant treatment in patients not receiving an ACE inhibitor: mortality was significantly reduced and the within-trial costs were $929 lower on average [95% CI: -3,243 to $1,533]. The average within-trial survival benefit among patients treated with valsartan was estimated at ~2.2 months. When evaluating variability associated with these estimates, in 78.0% of the 1,000 bootstrap replicates, valsartan was less costly while reducing mortality. In an additional 17.9% of the replicates, an ICER of less than $10,000/LYS was computed. When combining these results, in 95.9% of bootstrap samples, treatment with valsartan was either cost-saving or had an ICER below $10,000/LYS.
Conclusions: Inhibition of the renin-angiotensin system with valsartan was shown to be a dominant or economically attractive therapy in patients not taking ACE inhibitors.

810 Drug-eluting stents in coronary artery disease: assessment of outcomes and cost effectiveness

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Objectives: Restenosis limits the long-term success of coronary angioplasty in patients with coronary heart disease. Drug-eluting stents have been associated with very low restenosis rates (RAVEL and FIM trials). We assessed the economic value of the Sirolimus-eluting Bx-VELOCITY TM stent (CYPHER TM) in different indications with a high restenosis rate, with Belgium as case country.
Research design and methods: A decision model was developed to predict the 1-year cost-effectiveness comparing balloon angioplasty, conventional stenting, coronary artery bypass grafting (CABG) and CYPHER TM-stenting. Three indications were studied: small-diameter single-vessel disease, long single-vessel lesions and multi-vessel disease. Clinical data were obtained for small-diameter single-vessel from the RAVEL trial; for multi-vessel disease from the ARTS trial; and for long-lesions from a published clinical model. Given the experience with the RAVEL and FIM trials, the relative risk reduction in clinically driven re-intervention rate with CYPHER TM versus conventional stenting was assumed to be 95% for long lesions and equivalent to CABG for multi-vessel disease. Incremental cost-effectiveness is expressed as cost per revascularisation avoided.
Results: At a cost of 2,300 Euro per CYPHER TM-stent, incremental cost-effectiveness of CYPHER TM-stenting compared to conventional stenting varies between 1,119 Euro/revascularisation avoided in small-diameter single-vessel disease (see table) to 2,947 Euro in long-lesions. In multi-vessel disease CYPHER TM-stenting is dominant over CABG.

	Acute	Follow up	Total Cost	Incr. costs	Revasc.	Avoided	ICER
BALLOON	3914	1665	5579	-382	0.2651	-0.0414	9227
STENT	4586	1374	5960	–	0.2237	–	NA
CYPHER	910	285	6195	235	0.0139	0.2099	1119
CABG	12264	141	12405	6445	0.0400	0.1837	35075

ICER = incremental cost effectiveness ratio (cost per avoide revascularisation)

Conclusions: With the currently available data and applied profile, CYPHER TM-stenting is cost-saving in multi-vessel disease, and cost-effective in small-diameter and long single-vessel lesions.

811 Cost and cost effectiveness at 1 year in the stent or surgery trial (SoS)

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Background Randomised trial data showed that balloon angioplasty had lower initial hospitalisation costs compared to coronary artery bypass grafting (CABG) but has higher down stream costs due to the increased need for repeat revascularisation. Stents add to the initial cost of angioplasty, but by reducing repeat revascularisation may make PTCA both more clinically and economically attractive. We compared the cost and cost effectiveness of CABG and percutaneous coronary intervention with stents (PCI).
Methods SoS is a multi-national randomised trial involving 53 centres in Europe and Canada. Patients with multi-vessel coronary disease who were accepted by the interventionist and the surgeon for coronary revascularisation were eligible. Cost is based on detailed resource use in both initial and additional revascularisations, on hospital length of stay (LOS) at the initial procedure and all follow up hospital admissions, complications (MI, stroke, bleed) and cardiac medications at UK costs. 'Quality adjusted life years (QALYs) were estimated from individual patient survival and EQ-5D classifications at 3 timepoints, valued using UK population health state utility values. Cost effectiveness was measured in cost per life year gained and cost per QALY gained.
Results A total of 988 patients were randomised: CABG group 500, PCI group 488. The initial hospitalization costs were higher in the CABG group compared to PCI: £7,316 versus £3,844 (difference = £3,471, 95% CI £3,071 to £3,880). At one year the cost difference narrowed but remained higher for CABG £8,900 versus PCI £6,257 (difference = £2,643, 95% CI £1,814 to £3,343). The incremental cost effectiveness ratio (ICER) for CABG compared to PCI is £192,474 per life year gained (95% CI £77,377 to £1,085,464). The cost utility of ratio of CABG compared to PCI is £1,719,582 per QALY gained (95% CI inestimable).
Conclusion Over a one year time period CABG is more expensive than PCI and offers little added benefit in terms of QALYS. It appears that the additional initial cost of CABG could only be justified if there were continued and significant cost savings compared to PCI with stents in subsequent years.

812 Australian analysis of the HOPE study: clinical and economic benefits of ramipril in terms of events avoided and the cost/life year saved

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Objective: From an Australian perspective, to assess the clinical and economic impact of the use of daily ramipril 10 mg over a period of 5 years in an at-risk population as described in the groundbreaking Heart Outcomes Prevention Evaluation (HOPE) study.
Methods: Clinical benefits. To assess the clinical benefits, the result for each endpoint as reported in the HOPE paper (cardiovascular death, myocardial infarction, stroke & revascularisation) is converted to number-needed-to-treat (NNT). NNT is the reciprocal of the absolute risk reduction. The at-risk population, as defined by the HOPE investigators, was estimated nationally and per typical general practitioner from the relevant Australian statistics. The at-risk population is then divided by the NNT to estimate the potential number of strokes, CV deaths, MIs and revascularisations avoided.
Methods: Economic benefits. To assess the economic benefits, an incremental cost-effectiveness analysis was conducted. The model considered the costs and cost offsets arising from ramipril use for the 5 year period of the study. Costs were those associated with ramipril treatment and pathology testing. Cost offsets were those associated with: 1) a reduction in the use of other ACE inhibitors, and 2) a reduction in the primary endpoints of MI and stroke and in the secondary endpoint of revascularisation. Life years saved was approximated by calculating the difference in total years survived between the ramipril and control arms of the study. Net costs divided by life years saved is the cost per life year saved and this is reported in Australian dollars.
Results: Clinical benefits. Based on an Australian population of ~615,000 appropriate at-risk people, the use of ramipril 10 mg daily for 5 years is estimated to potentially prevent 9188 strokes, 14658 myocardial infarctions, 14317 CABG/PTCA procedures and 12534 cardiovascular related deaths. For a typical Australian general practitioner who has ~38 appropriate at-risk people, just under 1 of each type of these events (stroke, MI, CV death & revascularisation) can potentially be prevented.
Results: Economic benefits. The incremental cost effectiveness analysis estimates the cost per life year saved to be $17,214.
Conclusion: Based on the HOPE study, we have assessed the clinical and economic impact of daily ramipril 10 mg in an at-risk Australian population over a 5 year period. Ramipril provides clinically significant benefit both nationally and per general practitioner at a cost per life year saved which is comparable to other interventions.

FUNDAMENTAL ASPECTS OF ATRIAL FIBRILLATION

813 Atrial remodelling in the goat due to chronic complete atrioventricular block

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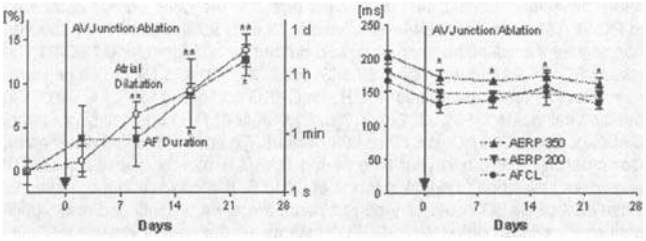
Atrial dilatation is an independent risk factor for the development of atrial fibrillation (AF) in humans. However little is known about the effects of chronic dilatation on atrial electrophysiology.
Methods: In 6 goats we implanted 2 atrial and 1 ventricular screw-in lead. At the tip of each atrial lead we mounted a pair of sonomicrometer crystals to measure the right atrial diameter. After a control period of 2 weeks (sinus rhythm, 120 bpm), radiofrequency ablation of the atrioventricular junction was performed and a stable ventricular escape rhythm of 50 bpm occurred. Atrial diameter, atrial refractory period (AERP), AF cycle length (AFCL) and the duration of AF episodes induced by burst stimulation were measured during 3 weeks of complete AV block.
Results: Chronic complete AV block caused progressive atrial dilatation up to 14% after 3 weeks (Fig. 1). Parallel to the increase in atrial size the duration of induced AF episodes prolonged from 13 seconds to more than 8 hours. Two days after AV junction ablation both AERP and AFCL decreased, but they kept constant during the following 3 weeks (Fig. 1).



Conclusions: Chronic AV block in the goat results in progressive atrial dilatation and prolongation of AF episodes. Shortening of the atrial effective refractory period (electrical remodeling) cannot explain the prolonged AF duration. The high correlation between atrial dilatation and AF duration suggests that atrial dilatation per se plays an important role in the creation of a substrate of persistent AF.

814 Gene expression profiling of human myocardium with atrial fibrillation by DNA microarray analysis

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Background - The molecular mechanism causing atrial fibrillation in human myocardium remains incompletely defined. We here used powerful DNA microarray technology for transcriptional profiling of genes induced in atrium of the patients with atrial fibrillation.
Methods - We used right atrium of patients who underwent cardiac surgery. On the basis of electrocardiographic findings, the patients were divided into 2 following groups: sinus rhythm group (n=10) and atrial fibrillation group (n=7). Expression profiles of 12000 human genes using the Affymetrix GeneChip (Human Genome U95A) were investigated with mRNA obtained from the atria. Quantitative analysis of selected genes was performed by the real-time PCR method.
Results - In the atrial fibrillation group, 33 genes including an ion channel, an antioxidant, an inflammation, 3 cell growth/cell cycle, 3 transcription, several cell signaling and several protein genes, and 7 expressed sequence tags (ESTs) were significantly activated (>1.5 fold, $p<0.05$) compared with those in sinus rhythm group. In contrast, 63 genes including several cell signaling/communication such as sarcoplasmic reticulum Ca2 ± ATPase 2, several cellular respiration and energy production and 2 antiproliferative or negative regulator of cell growth genes, and 22 ESTs were decreased (<0.5 fold, $p<0.05$) compared with those in sinus rhythm group.
Conclusion - These findings suggest that these genes may play critical roles in the initiation or the persistence of atrial fibrillation and pathophysiology of atrial remodeling.

815 Atrial expression of matrix-metalloproteinases in fibrillating human atria

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Background: Atrial tissue from patients with atrial fibrillation (AF) shows significant structural changes like fibrosis and degenerative alterations. In this setting, remodeling of the extracellular matrix by matrix metalloproteinases (MMP) may contribute to changes in atrial size and mechanical function. The purpose of the present study was to quantify atrial MMP expression in patients with and without AF.
Methods: Right atrial tissue samples from 28 patients undergoing open-heart surgery were examined. Fourteen patients had chronic persistent AF (> 6 months), the remaining 14 patients were in sinus rhythm (SR). Atrial expression of matrix metalloproteinases (MMP)-1, MMP-2 as well as TIMP-1 (tissue inhibitor of metalloproteinase-1) was quantified at the protein level by Western blotting. MMP-1 (collagenase) activity was analyzed by zymography. Immunohistochemistry was used to localize MMP expression in the tissue samples.
Results: Baseline clinical parameters were comparable in the two groups. The left atrial diameter was significantly increased in patients with AF (AF: 4.9 ± 0.2 cm vs. SR: 4.3 ± 0.2 cm; $p<0.05$). MMP-1 and MMP-2 were predominantly expressed in atrial fibroblasts and myocytes in both groups. The amount of MMP-1 protein was significantly reduced in patients with AF (SR: 5.3 ± 0.68 U vs. AF: 2.79 ± 0.60 U; $p<0.05$). In addition, the collagenolytic MMP-1 activity was also lower in fibrillating atrial tissue (SR: 1.73 ± 0.43 ng/μg protein vs. AF: 0.74 ± 0.17 ng/μg protein; $p<0.05$). In contrast, the amounts of MMP-2 (SR: 1.13 ± 0.2 U vs. AF: 0.93 ± 0.20 U; p=ns) and TIMP-1 (SR: 1.06 ± 0.20 U vs. AF: 0.82 ± 0.30 U; p=ns) were similar in both groups.
Conclusions: AF is associated with down-regulation of atrial MMP-1 activity. Reduced collagen degradation by collagenase may contribute to the structural remodeling and collagen accumulation in fibrillating human atria.

816 The degree of left ventricular hypertrophy predicts the incidence of atrial fibrillation

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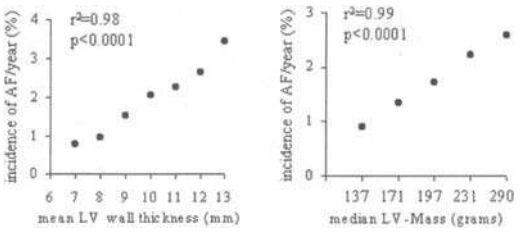
Introduction: In population based studies, the presence of left ventricular hypertrophy is being associated with the development of atrial fibrillation. We further explored a possible "dose-response" relationship between the degree of left ventricular hypertrophy and the incidence of atrial fibrillation.
Methods: From a computerized database which contains the results from all echocardiograms (including rhythm notation) that were performed in our institution from 1986 until present, we retrieved all patients with multiple examinations and sinus rhythm during the first ultrasound. The development of atrial fibrillation during the latest echo was evaluated in relation to left ventricular wall thickness at presentation.
Results: In total 8056 patients were studied, their mean age was 58 ± 15 years, there were 4579 males. 514 Patients developed atrial fibrillation during a median follow-up between the 2 ultrasounds of 37 months, range 1 to 194 months. There appeared to be a strong correlation between the mean value of the septal and posterior left ventricular wall thickness and the incidence of atrial fibrillation during follow-up (see Figure 1). The same is true for the correlation between subsequent quintiles of left ventricular mass and the incidence of atrial fibrillation (see Figure 2).



Conclusion: There is a strong linear correlation between the degree of left ventricular hypertrophy and the incidence of atrial fibrillation. Future studies are needed to clarify the mechanism behind this relation.

817 Connexin 40 is decreased in the right atrium of patients with persistent atrial fibrillation

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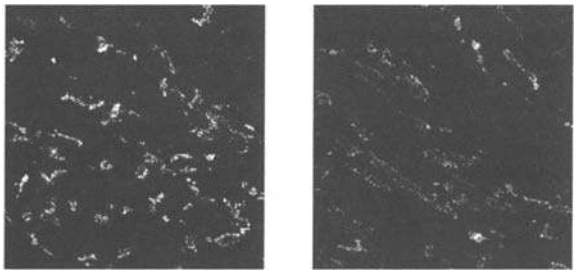
Introduction: Altered expression of gap junction proteins (connexins, Cx) lead to abnormal electrical coupling between cardiomyocytes. Goats with pacing-induced atrial fibrillation (AFib) showed marked inhomogeneities in the pattern of Cx 40 distribution. We studied the distribution of Cx 40 and 43 in patients (Pts) scheduled for heart surgery.
Methods: Samples of right atrial appendages were frozen in liquid nitrogen. Sections of 10 μm were incubated with antibodies against Cx 40 or 43, stained with an Alexa Fluor 660 dye and examined with a confocal laser scanning microscope.
Results: Patient data and Cx distribution are presented in the table. Cx 40 was significantly decreased in Pts with persistent AFib compared to SR. There was no significant difference between Pts with intermittent or postoperative AFib.



Cx 40 in SR (left) and AFib (right).

Patient data and Connexin distribution.

	Group 1	Group 2	Group 3	Group 4
n	20	12	4	12
age	65±10	69±9	76±3	72±6
atrial size>45 mm (%)	5	50 *	25	17
Cx 40 (%)	3,7± 1,6	2,0±0,9 *	4,3±2,1	2,8±1,9
Cx 43 (%)	4,1±2,0	3,7±1,7	4,6±0,8	5,0±1,7

Group 1: Pts with SR,Group 2: Pts with persistent AFib>3 month,Group 3: Pts with intermittent AFib and preoperative SR,Group 4: Pts with postoperative AFib. * p<0,05

Conclusion: Decreased amounts of Cx 40 might contribute to the maintenance of AFib due to microheterogeneities in conduction velocity.

818 Correlation between the human sinoatrial node and the crista terminalis in the posterior right atrium

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Background: Several recent observations have suggested that conduction block or penetration of crista terminalis (CT) influence the type of atrial flutter and its perpetuation. The anatomical relationship of the CT and the sinoatrial node (SN), known as a structure adjacent to CT has not been fully understood in particular regarding its inferior margin. We examined the distribution of SN along CT in order to clarify the anatomical relevance to myocardial connection of the posteromedial right atrium.
Methods: Eighteen autopsied hearts aged 31 to 89 years (mean 64.0 years, 10 male and 8 female) were studied. None of the cases showed conspicuous supraventricular arrhythmia. The whole length of CT was excised after fixation with formaldehyde and cut perpendicular to the longitudinal axis into 10 mm thick slices. Each tissue sample was serially sectioned at a thickness of 10 micrometer and every 100th section was stained. We measured and reconstructed the distribution of SN on the endocardial aspect of the right atrium.
Results: The length of the SN ranged from 11 to 40 mm (mean 22 mm) and that of CT was from 26 to 60 mm (mean 44 mm). The SN usually located between CT and the posterior wall of the right atrium, and distributed from 24.4 to 85.7% (mean 52.6%) of the whole CT length. In many cases, the SN was adjacent to thick musculature of CT throughout its whole length, but in some cases the junction to the posterior right atrial myocardium showed fibrofatty replacement.
Conclusion: The distribution of the SN was highly variable and its length was unexpectedly long in some patients. This diversity of the length of the SN likely influences the conduction across the CT of patients with typical atrial flutter.

ATRIAL FIBRILLATION BURDEN REDUCTION BY PACING

819 Suppression of paroxysmal atrial fibrillation by a dedicated pacemaker: correlation between atrial tachycardia burden and quality of life

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Recently, pacemakers with specific algorithms for suppression and atrial overdrive pacing therapy (DDDRP) in patients (pts) with paroxysmal atrial fibrillation (pAF) have been introduced. Preliminary results have demonstrated a reduction of atrial arrhythmia frequency with activation of the dedicated algorithms and beneficial effects on quality of life (QoL) in selected patients. The contribution of pAF, and the effects of DDDRP on the overall QoL in these patients, however, remain ill defined.
Methods: Consecutive pts with a class I indication for DDD pacing (P-ind) and prior documentation of pAF were implanted with a DDDRP device (Medtronic AT500). Atrial tachycardia burden (AtB) was defined as the percentage of total time while a patient suffers from pAF according to the monitored and stored electrograms of the device. All pts completed the short form health survey questionaire (SF-36) at implant, at 3 months (mo), and 12 mo follow-up.
Results: Data from 41 pts (60% male; mean age 68±9 years) were analyzed. Mean values for AtB remained unchanged with DDDRP from 8±15% at baseline to 9±17% at 3 mo and 13±27% at 12 mo (p=0.24). In 12 pts, a reduction in AtB occurred, AtB remained unchanged in 10 pts, while 19 pts had an increase of AtB during follow-up. In contrast to AtB, the mean value of 6/8 subscales of SF-36 significantly improved from implant to 3 mo follow-up, and remained stable until one year thereafter. Individual improvements on SF-36 were comparable in pts showing a reduction in AtB compared to non-responders. Pearson analysis found no correlation between AtB and any subscale of SF-36 at baseline or during follow-up.
Conclusion: The reduction of AtB in a subset of patients during 12 months after DDDRP implantation does not significantly impact on QoL according to SF-36. In pts with established P-ind, the observed improvement in QoL seems to be dominantly caused by the effects of antibradycardia pacing therapy.

820 Prevention of atrial fibrillation by DDD+ atrial overdrive pacing: final results of a randomized crossover study

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Introduction: Dynamic atrial overdrive stimulation at a rate slightly above the intrinsic rate is a newly proposed method to suppress recurrences of atrial tachyarrhythmia (AT) in pacemaker (PM) patients (pts). Our study evaluated clinical efficacy of the DDD+ overdrive mode implemented in dual-chamber Inos2 CLS PMs (Biotronik, Germany).
Methods: 100 pts with paroxysmal AT and conventional pacing indications (71% SSS, 25% AVB) were randomized in 19 clinical centers to DDD+ or conventional DDD mode at 3 months after PM implantation. A bipolar atrial lead was placed in the right appendage (60%) or laterally (40%). The basic rate was programmed to 61.5 ± 4.3 bpm. Upon sensing an atrial event, the DDD+ mode increased the pacing rate by 8 ± 2 bpm (programmed range 4-12), which was followed by 1 bpm rate decrease after each 20 ± 3 atrial beats. Mode crossover took place 6 months after randomization and the pts were followed for additional 6 months in the other mode. The cumulative duration of sustained (>60 s) AT episodes was extracted from the PM memory and compared for the two modes on intrapatient basis (paired two-tailed t-test). The comparison was made for the entire study population as well as for different subgroups of pts in order to evaluate clinical predictors of the overdrive therapy outcome.
Results: Crossover data were collected in 75 pts; the remaining 25 pts were drop-outs. The percentage of atrial pacing (AP%) was increased from 58±32% (DDD) to 95 ± 11% (DDD+, p<0.001), and the mean heart rate from 66.9±6.1 bpm (DDD) to 72.8±7.8.bpm (DDD+, p<0.001). The AT burden in the entire population was reduced by 26%, from 16.3 (DDD) to 12.0 hours/wk (DDD+, p=0.066). In 32 pts with AT burden >2% of time, the reduction was 28%, from 37.8 (DDD) to 27.0 h/wk (DDD+, p=0.044). The subgroups of pts with the most significant reduction in AT burden by overdrive pacing were: 50 pts with <80% of AP% in DDD mode: 16.1 (DDD) vs 8.8 h/wk (DDD+, 45% reduction, p=0.016), 25 pts with the basic rate set to 65-75 bpm: 29.0 (DDD) vs 16.6 h/wk (DDD+, 43% reduction, p=0.011), and 37 pts who did not use class II antiarrhythmics: 18.2 (DDD) vs 9.2 h/wk (DDD+, 50% reduction, p=0.021). In the complementary groups to these 3 subgroups, there was no additional benefit of DDD+ over DDD pacing (0-11% reduction in AT burden, p-values 0.57-0.95).
Conclusions: The DDD+ overdrive pacing exerted comparatively strongest antiarrhythmic effect (vs. DDD pacing) in pts paced <80% of time in the DDD mode, in pts with basic rates set to 65-75 bpm, and in pts using no Class II antiarrhythmics.

821 Can we reduce atrial fibrillation by atrial overdrive pacing? Lessons from conventional DDD antibradycardia pacing

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The objective of the study was to evaluate the effectiveness of atrial pacing in the prevention of AF in patients with conventional DDD antibradycardia pacing.
Methods: 52 patients (66 ± 11 years) with dual chamber pacing (Vitatron, "Selection" Series) and a history of paroxysmal AF were included. AF preventive algorithms including atrial overdrive pacing ("PACE Conditioning") were switched off. The data obtained by the PM diagnostic features after a mean follow-up of 96 ± 28 days include: (1) number of premature atrial contractions per hour (PAC's/hour), (2) total AF burden (% of storage period), (3) mean episode duration (hours), (4) number of AF episodes/day, (5) percentage of atrial pacing. According to the frequency of atrial pacing the patients were divided into Group A (atrial pacing rate >50%) and Group B (atrial pacing rate <50%).
Results: Patients with a high rate of atrial pacing (Group A) not only presented significantly smaller numbers of PAC's/h during sinus rhythm (26.3 ± 27.3 vs. 100.8 ± 184.5, $p<0.05$), but also a significantly lower total AF burden (7.4 ± 13.5% vs. 25.0 ± 31.1%, $p<0.01$) and shorter mean AF episodes (1.2 ± 2.2 h vs. 9.0 ± 20.4, $p<0.05$). The number of AF episodes/day did not differ significantly between both groups (2.0 ± 3.4 vs. 2.8 ± 4.1, $p=0.46$).
Conclusions: 1. Atrial pacing during conventional DDD pacing reduces the PAC activity during sinus rhythm, total AF burden and duration of the AF episodes but not the AF recurrence rate. 2. These results may be explained by an electrical substrate modulation due to atrial pacing. 3. We conclude that "permanent" atrial overdrive pacing is suited for the AF preventive therapy, preferentially in patients with a low atrial pacing rate during conventional DDD pacing. Yet, the impact of overdrive pacing on the AF recurrence rate has still to be studied.

822 Comparison of atrial overdrive, DDDR and CLS pacing in reducing atrial fibrillation burden in Brady-Tachy syndrome patients

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Standard atrial overdrive pacing algorithms have been designed to reduce Atrial Fibrillation (AF) recurrences in patients (pts) with Brady-Tachy Syndrome (BTS); however they do not provide physiological rate modulation. The aim of this study is to compare atrial pacing percentage (AP%) and AF Burden, measured as time spent in AF, in BTS pts treated with conventional DDDR pacing, DDD+ overdrive or physiological Closed Loop Stimulation (CLS). We present a preliminary data analysis of the study. Methods: 131 BTS pts (72 female, mean age 76±9), received a dual chamber pacemaker (Philos DR, Inos2+, Biotronik). Ischemic heart disease was present in 12% of pts, hypertension 47% and other or no heart disease in 41%. After the first month, pts were randomized to DDDR, DDD+ or CLS pacing, and controlled at 4- and 7-months. At each follow-up AP% and AF Burden were analysed using F test or Kruskal-Wallis test, where applicable, and SNK test for multiple comparisons.
Results: (see table below). At 4-month follow-up (47 pts) AP% was significantly higher in CLS and DDD+ groups compared to DDDR group. This difference was not confirmed at 7-month follow-up (26 pts) but AP% in CLS group remained higher than in DDDR group. AF Burden, as expected, showed a great variability among groups. However, although not statistically significant ($p=0,08$ at 4-months and $p=0,12$ at 7-months), CLS mode was associated with a markedly lower AF Burden trend at both follow-up visits.

AP% and AF Burden

4 month follow-up	AP%	AF Burden (min/day)
DDDR (N=17)	78 ± 24 *^	86±199 (8%±16%)
CLS (N=13)	92 ± 18 ^	17±59 (2%±7%)
DDD+ (N=17)	94 ± 14*	154±303 (11%±17%)
7 month follow-up	AP%	AF Burden (min/day)
DDDR (N=10)	68 ± 25	130±302 (9%±17%)
CLS (N=7)	79 ± 17	6±15 (4%±9%)
DDD+ (N=9)	93 ± 9	178±417 (14%±20%)

*$p<0,05$, ^$p<0,05$

Conclusions: In BTS pts: 1. CLS and DDD+ pacing are associated with a higher AP% than DDDR pacing; 2. CLS pacing shows a better trend in terms of AF Burden Compared to the DDDR and DDD+ pacing; 3. These preliminary results seem to support the use of physiological heart rate modulation (CLS pacing) in the treatment of BTS pts.

823 Significant reduction of AF burden by the AF suppression™ algorithm

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Introduction: Successful suppression of paroxysmal atrial fibrillation (PAF) using the AF Suppression™ algorithm (St. Jude Medical) has been studied. AF Suppression™ paces the atrium just above the patient's natural circadian rate without employing a fixed high rate.
Methods: The international, multi-center ADOPT-ALL study is a prospective, randomized, single-blinded cross-over, study of 250 patients with history of PAF. The objective was to investigate whether DDDR pacing with the AF Suppression™ algorithm could reduce episodes of atrial fibrillation more effectively than DDDR pacing alone (as Auto-Mode-Switch (AMS) burden and AF burden).
Results: Presently 230 patients are enrolled internationally, 75 patients in the Austrian centers, 44 Austrian patients with a stable anti-arrhythmic drug regimen have finished the 6 month follow-up. The reduction of mean AMS burden and mean AF burden has been calculated (Table 1) as well as the percentage of atrial pacing and the mean heart rate (Table 2).

Table 1. Mean AMS and AF burden in % of total follow-up time

	AF Suppression OFF	AF Suppression ON	Reduction in %	p-Value
Mean AMS burden (n=44)	6,9	3,5	49,4	<0,04
Mean AF burden (N=44)	6,6	3,0	54,0	<0,04

Table 2. Mean heart rate in /min

	AF Suppression OFF	AF Suppression ON	p-Value
% of atrial stimulation	68,15 ± 28,0	95,03 ± 11,7	<0,00001
Mean heart rate	68,74 ± 7,0	70,68 ± 7,6	n.s.

Conclusion: These results show that the AF Suppression™ algorithm reduces significantly mean AMS burden and mean AF burden in patients with sinus node dysfunction and paroxysmal or persistent atrial fibrillation. The percentage of atrial stimulation was highly increased (by about 40%) nevertheless the mean heart rate did only slightly increase (2.8%). The AF Suppression™ algorithm was very well tolerated by all patients and has not been turned off in any patient.

824 Effect of pacing for prevention and termination of atrial tachyarrhythmias on arrhythmia burden over a 12 month period

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Atrial pacing techniques are being used for prevention and termination of atrial tachyarrhythmias (ATs). The present study analyzed the effect of 3 combined algorithms for AT prevention together with atrial antitachycardia pacing (ATP) on the time that the patient (pt) spends in AT (AT burden).
Methods: In pts with a conventional pacing indication and ATs, a DDDRP pacemaker (AT500, Medtronic Inc, MN) was implanted. Memory functions for AT episodes (atrial electrograms, marker annotations) and AT burden were activated after implantation. After 1 month, reliability of AT detection was assessed on the basis of stored annotated atrial electrograms, and algorithms for AT prevention (continuous overdrive, atrial rate stabilization, post mode switching overdrive) and atrial antitachycardia pacing modes (burst, ramp) were activated. Devices were interrogated after 1, 3, 6 and 12 months. At 12 months, AT burden was classified into 6 groups: 1. 0% (no AT episodes after activation of preventive pacing), 2. less or equal to 1%, 3. 1-99% with constant decrease, 4. 1-99% with no change, 5. 1-99% with constant increase, 6. 100% (persistent for the final 6 months).
Results: In 60 pts (sick sinus syndrome 39, AV block 12, binodal disease 2, planned AV node ablation 7, carotid sinus syndrome 1) and ATs (atrial fibrillation 54, atrial flutter 22, ectopic AT 3) which were persistent in 27 pts, mean AT burden was 12 ± 24% after 1 month (no preventive pacing) and 14 ± 29% after 12 months. Twenty pts (33%) had no AT episode, in 10 pts (17%) AT burden was less or equal to 1%. In 9 pts (15%), the AT burden was 1-99% and showed a constant decrease, in 7 pts (12%) it remained unchanged, and in 10 pts (17%) it increased continuously. Four pts (7%) had a progression to permanent AT.
Conclusion: In approximately 1/3 of pts, pacing for prevention of AT completely suppressed AT. Another 1/3 responded well to pacing with an AT burden less or equal to 1% or a constant decrease of AT burden. In 1/3 of pts, AT burden was unchanged or even increased despite these pacing techniques.

WE ARE STILL ON THE WAY: DRUG ELUTING AND COATED STENTS

861 Oral rapamycin to inhibit restenosis in de novo coronary lesions requiring stenting: the ORBIT study

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Background: Drug-eluting stents (utilizing antiproliferative agents such as Rapamycin) have shown the ability to limit restenosis. Oral Rapamycin(R)is an alternative delivery strategy that can target all stenosed coronary segments and is potentially more cost effective. Methods: The Oral Rapamycin to inhiBIT restenosis (ORBIT) study consists of a 50 patient (pt) registry for de novo coronary artery stenosis treated with stent implantation in up to 2 vessels. The first 30 pts receive R 2 mg/day for 30 days, then 20 pts R 5mg/day for 30 days, after all pts receive a 5mg oral bolus on day of the procedure. Results: We report an interim analysis of the first 30 pts (age 60 ± 10 years, 14% diabetes) enrolled (R 2mg/d). The mean number of treated lesions per pt was 1.3 ± 0.5, with reference vessel diameter 3.2 ± 0.4 mm and mean lesion length of 21.3 ± 10.5 mm. Angiographic success was achieved in all pts. Mean pre-discharge serum R levels is 3.4 ± 2.4 ng/ml (range 1.0- 8.4). No in-hospital events were noted apart from one patient with post-procedural CKMB rise > 3x normal. One patient was dropped after the initial loading dose of R. One pt ceased R after 7 days due to gingival bleeding and 5 pts have had diarrhea, which has resolved on discontinuing the treatment. To date, 24 pts (83%) have completed 30-day treatment with no reported sepsis at a mean follow-up of 56.6 ± 30.7 days. No patient has required repeat PCI since study enrollment. Conclusions: Oral Rapamycin administration for prevention of restenosis is safe and feasible. Complete 6-month clinical and angiographic outcomes will be available at presentation.

862 Persistent inhibition of neointimal hyperplasia after sirolimus eluting stent implantation: long-term (18 months) clinical and 3D-IVUS follow-up

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Background: The early results (4-12 months) of sirolimus eluting stent implantation showed a near complete abolition of neointimal hyperplasia. However the question remains whether the early promising results will persist at long term follow-up. The objective of our study was to evaluate the safety and efficiency of sirolimus eluting stent implantation at 18 months follow-up.
Methods: Fifteen patients with de-novo coronary artery disease were treated with 18mm sirolimus-eluting Bx VELOCITY stents (Cordis Waterloo, BL), loaded with 140 μg sirolimus/cm^2 metal surface area in a slow release formulation (>28 days drug release). Motorized pullback IVUS was performed post procedure and at 6M and 18M FU. Vessel volume, stent volume, neointimal hyperplasia (NIH), and % obstruction volume was calculated.
Results: Sirolimus eluting stent implantation was successful in all 15 patients. During the in-hospital course, 1 patient died of cerebral haemorrhage. At 18 month repeat catheterization performed in 8 of 14 eligible patients (6 asymptomatic patients refused). Through 6 months follow up and up to 18 months no restenosis and additional event occurred. In 2 patients, additional stenting was performed at 18 M FU due to significant lesion progression remote from the Sirolimus stent. 3-D IVUS showed no significant deterioration in lumen volume (see table). No edge effect was observed. Proximal and distal edge lumen volumes were calculated 44.0 ±17.6 mm^3 and 34.9±12.2 mm^3, at 6 month versus 42.7 ±19.9 mm^3 and 33.3±16.4 mm^3 at 18 M follow-up, respectively P=NS).

3D IVUS results

	Post	6M	18M
Vessel Vol. (mm^3)	280.9±74.4	287.4±64.4	283.5± 70.2
Stent Vol. (mm^3)	130.7±32.5	132.6±32.2	130.7±30.1
Lumen Vol. (mm^3)	130.7 ±32.5	130.9±32.1	124.2±27.5
NIH Vol. (mm^3)		1.7±1.6	6.5± 5.2*
% Obstruction Vol		1.4±1.2	4.8±2.8*

*p<0.05 6M FU vs 18M FU (paired t-test)

Conclusion: Sirolimus eluting stents are safe and effective in single de-novo coronary lesions in preventing neointimal hyperplasia up to 18 months after stent implantation.The modest but significant increase in the NIH warranted further careful quantitative IVUS assessment at 24, 36, 48 month follow ups.

863 First clinical experience with a paclitaxel-derivate eluting polymer-stent system implantation for ISR: immediate and long-term outcome

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Background: It has been shown that antiproliferative drugs, such as paclitaxel, lower the amount of intimal hyperplasia following stent implantation. We report the first clinical experience of 7-hexanoyltaxol (QP2) eluting polymer stent system (QuaDS) implantation for in-stent restenosis.
Methods and Results: Fifteen consecutive patients with elective indication to percutaneous coronary intervention (PCI) for in-stent restenosis were treated with the QuaDS-QP2 stent implantation. Sixty percent of lesions had an ostial-proximal location and diffuse ISR pattern was present in 46.6% of target lesions. 30% of the patients had three-vessel disease and multivessel intervention was performed in 5 patients. Among these patients, the QuaDS-QP2 stent was implanted only in one of the treated vessels. The QuaDS-QP2 stent was successfully implanted in all target lesions except for two lesions where the restenotic segment could not be completely covered by the stent. One patient suffered from post-procedure non-Q wave myocardial infarction (NQWMI). No other adverse events were observed during hospital stay. Six and twelve months angiographic and clinical follow-up was scheduled for all patients. At 6 months three patients had target lesion revascularization (20%). Two patients had restenosis (13.3%). One of them in a gap between two drug-eluting stents, and the other one had stent occlusion leading to NQWMI two months after the procedure. Minimal intimal hyperplasia was observed in all the segments covered by drug-eluting stents (late loss = 0.47±1.01 mm with a loss index = 0.17±0.39). At 12 months, one patient suffered from NQWMI and 8 out of 13 patients (61.5%) had angiographic restenosis (late loss = 1.36±0.94mm with a loss index = 0.62±0.44).
Conclusion: This first experience with QuaDS-QP2 stent implantation for in-stent restenosis revealed minimal intimal hyperplasia at 6-month follow-up. However, the antiproliferative effect was not maintained at 12-month follow-up resulting in delayed occurrence of angiographic restenosis. We cannot exclude a possible late inflammatory reaction to the polymer carrier as an explanation for these failures.

864 Sirolimus-eluting stent for treatment of in-stent restenosis: the first European clinical experience

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Background: Recent trials indicated that the use of Sirolimus eluting stents(SES)was safe and effective in inhibiting in stent neointimal hyperplasia in de-novo lesions.The aim of our study is to evaluate the safety, feasibility and clinical outcome (280days) of SES in patients with ISR.
Methods: Pts with recurrent ISR (>50%DS)in a native coronary artery and objective evidence of ischemia were included to receive an 18 mm sirolimus-eluting Bx VELOCITY stent(Cordis). QCA and 3D-IVUS follow-up was performed at 4M. Vessel volume,lumen volume, stent volume, % in-stent volume obstruction(PIVO)(SV-LV/SV*100)were calculated. Late lumen loss was defined as MLD post procedure-MLD FU.All pts received Clopidogrel 75 mg for 2M and Aspirin >75 mg indefinitely.
Results: SES implantation(n=24) was successful in all 15 patients. Baseline characteristics; DM 4/15,previous PCI per lesion 1.5± 0.9(range1-4),previous brachytherapy 4/15. Types of ISR; 8pts type I-II and 7pts type III-IV.In hospital course was uneventful. One pt died (sudden death) 3.5M after stent implantation. Only 1 pt showed repeat restenosis with silent total re-occlusion at 4M FU angiography.In the remaining pts (n=13),late lumen loss was 0.09 mm.IVUS FU were obtained in 12 pts. One patient with 5 eluting stents shows no sign of stenosis (3.4 PIVO) at 4m FU IVUS, developed acute occlusion 3 weeks after discontinuing clopidogrel.The pt was successfully treated by thrombus aspiration and re-PTCA. In addition, 1pt who had undergone two bypass surgery, 3 times repetitive in stent re-stenosis and no NIH (2.2PIVO)in the SES at 4M FU IVUS,died due to congestive heart failure 9.5M after the index procedure.

4M Follow-up 3D-IVUS results

N=12	POST	4M FU
Vessel Volume (mm^3)	370.9 ± 130.2	371.2 ± 134.7
Stent Volume (mm^3)	156.1 ± 58.4	157.6 ± 64.3
Lumen Volume (mm^3)	156.1± 58.4	151.4 ± 62.5
% Obstruction Volume		3.9 ± 3.4

Conclusion: Sirolimus eluting stent implantation in ISR lesions is feasible, safe and effectively prevents neointima formation even a patient population with highly complex lesions.

865 Can sirolimus-eluting stents prevent restenosis in diabetic patients? A subanalysis of the randomized, multi-center RAVEL trial

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Diabetic patients (pts) are prone to procedural complications and to a less favorable outcome after percutaneous coronary intervention (PCI) in comparison to non-diabetic pts.
We investigated the outcome of diabetics after implantation of sirolimus eluting stents.
We performed a subgroup-analysis of pts with diabetes mellitus who were prospectively included into the multicenter RAVEL trial. Pts with single de novo lesions were randomized to receive a 18mm sirolimus eluting (SES) Bx velocity™ stent (Cordis, Waterloo, Belgium) or a bare (BS) Bx velocity™ stent (Cordis, Waterloo, Belgium). Major adverse cardiac events (MACE) at 6 month follow up were defined as death, myocardial infarction (MI), target vessel PTCA and CABG.
QCA was performed by using the CAAS system.
Results: 44 Patients with diabetes mellitus were randomized into the RAVEL trial.

QCA

		SES (n=19)	BS (n=25)	p-value
Baseline	Lesion length (mm)	9,4 (3,2)	9,4 (2,4)	ns
	RD (mm)	2,52 (0,51)	2,51 (0,47)	ns
	MLD (mm)	0,99 (0,24)	0,93 (0,33)	ns
	DS (%)	60 (9)	63 (10)	ns
Post	MLD (mm)	2,37 (0,43)	2,36 (0,45)	ns
	DS (%)	13 (6)	14 (9)	ns
6m FUP	MLD (mm)	2,31 (0,40)	1,56 (0,64)	< 0.001
	DS (%)	16 (5)	38 (21)	< 0.001
	Late loss (mm)	0,08 (0,20)	0,82 (0,53)	< 0.001
	Restenosis rate (%)	0	42	< 0.001

Mean (1 SD)

In the follow-up period, no pt (0%) of the SES group experienced a MACE, while 3 pts (12%) of the BS group had MACE (1 death, 1 MI, 1 PTCA).
Conclusion: Sirolimus eluting stents seem to favorably affect the outcome of diabetic patients. No MACE, no restenosis and only minimal late lumen loss was seen in our pts at 6 months follow-up. This might support the use of sirolimus eluting stents as first-line PCI strategy in diabetics.

866 Influence of stent coatings on acute and six-month clinical and angiographic outcomes in real world patients

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Purpose: To compare acute and six-month clinical and angiographic results of coated (C) (Carbostent and PC Biodivysio) and uncoated (UC) stents in a real world population.
Methods: From January 1999 to December 2000, 1544 pts underwent PCI with stent implantation: 590 pts had C stents and 954 pts had UC stainless steel stents according to operator preference. The two groups were matched in gender, age and major cardiovascular risk factors. Clinical indication for PCI were stable angina (68.8% C vs. 66.3% UC, ns) unstable angina (18.6% C vs 18.4% UC, ns) and AMI (8.8% C vs 12.3 UC, $p<0.001$). Multiple stents were implanted in 20% C vs 22.5% UC (mean stent/pt 1.4 ± 0.5 C vs 1.3 ± 0.6 UC, ns) respectively, while stent length was 21.6 ± 11.5 C vs 19.9 ± 8.3 UC (p=ns), and stent diameter was 3.6 ± 0.6 C vs 3.6 ± 0.58 UC.
Results: Angiographic success was obtained in 98% C vs 97% UC, death occurred in 0% C vs 1.2% UC, AMI in 2.8% C vs 2.5% UC, subacute stent thrombosis was 0% in C vs 0.6% in UC (all p=ns). Six-month follow-up clinical and angiographic data are shown in Table 1
Conclusions: Similarly high clinical and angiographic acute success was obtained with C and UC stents. No late thrombosis occurred in C pts, suggesting thromboresistant properties of C stents. Carbofilm and phosphorylcoline coated stents were associated with significantly lower restenosis rate in unselected real world patients, which likely resulted from reduced neointimal proliferation, as suggested by a lower loss index.

Table 1

	Coated	Uncoated	p value
N° pts	282	418	-
Death	0.3%	0%	ns
MI	0.3%	1.1%	ns
Angina/Ischemia	17.7%	20%	ns
Re-PTCA	14%	21%	ns
CABG	2.5%	2.4%	ns
Late Loss	0.88	1.10	0.02
Loss Index	0.38	0.55	0.002
Restenosis Rate	21%	32%	0.002

DRUG ELUTING STENTS: OPTIONS BEYOND SIROLIMUS?

867 A polymer-based copper coating can generate nitric oxide from S-nitrosoglutathione but does not induce significant neointimal formation

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Background: Current research is directed towards finding an agent that can be coated onto a stent to inhibit in-stent restenosis, a process which involves platelet, inflammatory cell and vascular smooth muscle cell responses. Nitric oxide (NO) is a potential candidate for this role, as it can theoretically inhibit all aspects of the vascular response to stent deployment, whilst enhancing endothelial cell regrowth.
S-nitrosothiols (RSNOs) are endogenous circulating NO donors. We have previously shown that NO can be generated from RSNOs by copper in a dose-dependent manner, to inhibit platelet aggregation in vitro.
However, copper-coated stents have been shown by others to induce severe inflammatory responses in the vessel wall. In order to coat stainless steel with small quantities of copper we have developed a novel polymer-based method. The coating, containing 5% or 20% copper (w/w), can be used to generate NO from RSNOs to inhibit platelet aggregation in vitro in a dose-response manner.
Methods and Results: Stainless steel discs were implanted into subcutaneous tissues in mice and inflammatory responses were assed by measuring histological tissue changes and macrophage acid phosphatase activity on the surface of the disc 7 days after implantation. The 20% copper coating induced significantly more inflammation than both the 5% copper and the polymer coating alone. There was no difference between the effects of 5% copper and the polymer itself.
The effect of the coating on the development of neointima was then tested in the porcine coronary artery model. Stents coated with the polymer-copper coating (1% and 5% copper (w/w); n = 6 per group) were deployed at a balloon artery ratio of 1.25:1. The vessels were harvested at 28 days and the resulting neointimal thickness compared with that seen following implantation of stents coated with polymer alone. Neointimal thicknesses (arbitrary units), corrected for vessel size and injury score, were 0.019 + 0.001, 0.032 + 0.009 and 0.021 + 0.001 for 1% copper, 5% copper and polymer alone respectively (mean + sem; p = 0.152, 1-way ANOVA).
Conclusions: NO can theoretically inhibit the process of in-stent restenosis. Copper can generate NO from RSNOs, but is inflammatory and pro-thrombotic. Stents coated with a polymer-copper mixture, at concentrations of copper that will inhibit platelet aggregation in vitro, do not induce significantly more neointimal formation in porcine coronary arteries than those coated with polymer alone. Thus it may be possible to use a polymer-copper-coated stent to generate NO within the coronary artery.

868 Latrunculin A inhibits smooth muscle cell proliferation and neointimal formation in a porcine coronary stent model

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Background: In-stent neointimal formation, predominantly due to smooth muscle cell (SMC) migration and proliferation, remains a significant limitation of coronary stenting. Latrunculin A (LA) is an inhibitor of the actin microfilament formation, thereby theoretically interfering with SMC migration and proliferation. This study evaluated the in-vitro and in-vivo effects of direct LA stent coating on in-stent neointimal formation in a porcine coronary model. Methods: In-vitro cell proliferation was assessed by means of a coulter counter after LA incubation (10^{-8} - 10^{-5} M) for 7 days with SMCs isolated from the rabbit aorta. Coronary stents (13 mm, Multi-Link Tristar ®, Guidant) were dipped in pure ethanol (control) or in a 1 mg LA/ml ethanol solution (treatment) and air-dried. Loading capacity and release in NaCl at 37°C were performed using UV spectrophotometry. Stents (12 control and 12 treatment) were then randomly deployed (oversize 1.1:1 to 1.2:1) in the right or left coronary artery of 12 crossbred pigs (weight 20 - 25 kg). The pigs were sacrificed after 6 weeks. Blinded quantitative coronary analysis (QCA) was performed before, immediately after stent implantation and at follow-up using the CAAS-II®-QCA-system. Blinded morphometry was performed on 5 μm cross-sections using stereological point counting. Results: LA inhibited SMC proliferation in a dose-dependent way (control: 1.82±0.21, 10^{-8} M: 1.84±0.07*, 10^{-7} M: 1.25±0.09*, 10^{-6} M: 0.35±0.10*, 10^{-5} M: 0.31±0.13*; data are x 10^5 cells/well; n=4; *p<0.01). Coated stents contained 1.53±0.12 μg LA (n=3). Complete release in-vitro was already achieved after 4 hours. QCA analysis at 6 weeks revealed a decreased late lumen loss (-0.03±0.20 vs 0.23±0.29: p<0.05) and percentage stenosis (15±5 vs 30±14: p<0.005) in the LA-coated stents. Morphometry showed a decreased intima/injury value (1.0±0.4 vs 1.3±0.8: p=0.08) in the LA-group. No thrombosis was found in either group. vWF immunostaining showed complete re-endothelisation at 6 weeks in both groups. Conclusion: In-vitro, latrunculin A inhibits SMC proliferation in a dose-dependent way. Direct latrunculin A stent coating reduces neointimal hyperplasia after implantation in healthy porcine coronary arteries in-vivo. These results warrant further studies of latrunculin A stent coatings.

869 Tacrolimus, but not sirolimus targets human vascular smooth muscle cells, but spares endothelial cells – Implications for drug-eluting stents

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Background: Excessive proliferation and migration of vascular smooth muscle cells (VSMC) plays a major role in the development of in-stent restenosis. Indeed, local antiproliferative strategies such as brachytherapy and, most recently, rapamycin-eluting stents have been shown to reduce the occurrence of restenosis. However, late thrombosis has emerged as a side effect in both clinical applications suggesting insufficient reendothelialisation. The ideal agent used for local drug delivery would exert strong antiproliferative action on VSMC while sparing endothelial cells (EC). Sirolimus (FK506) and tacrolimus (rapamycin) are potent antiproliferative and immunosuppressive agents that both bind to FK binding protein 12, but have different downstream targets. We investigated whether these drugs differ with regard to their effects on VSMC and EC.

Methods and Results: DNA synthesis using thymidine incorporation was determined after stimulating cultured human saphenous VSMC with PDGF-BB 5 ng/ml and EC with fetal calf serum 2% for 24 hours. A dose-response curve was characterized in the presence and absence of tacrolimus and sirolimus using drug concentrations ranging from 10E-12 to 10E-6 M (n>3 for each condition). The half maximal inhibitory concentration for VSMC (IC50) for tacrolimus was 5.1 x 10E-7 ± 4.3 x 10E-7 M and for sirolimus 4.1 x 10E-9 ± 2.9 x 10E-9 M. Compared to the IC50 in VSMC, the IC50 in EC was met only at higher concentrations for tacrolimus (3.3 x 10E-6 ± 2.5 x 10E-6 M), but at lower concentrations for sirolimus (7.1 x 10E-10 ± 1.7 x 10E-10 M).

Conclusions: Sirolimus is a more potent antiproliferative drug in VSMC than tacrolimus. Anticipating that the effective dose for targeting VSMC proliferation of tacrolimus can be achieved on a drug-eluting stent, the unwanted side effects on EC proliferation might be less with tacrolimus than with sirolimus. These findings suggest that on a drug-eluting stent, tacrolimus allows earlier endothelial regeneration than sirolimus and make it a promising candidate for local drug delivery.

870 Stent-based delivery of combined chemotherapy with cis-platinum and mitoxandrone in a porcine coronary model to prevent restenosis

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Background: Prevention of neointimal hyperplasia after stent implantation is a target for current cardiology. Drug-eluting stents, such as rapamycin-eluting stents have been proposed as means of preventing restenosis. However, combination of cytotoxic agents hasn't been used. The purpose of the present study was to compare the angiographic and histologic results of stent-based delivery of cis-platinum in combination with mitoxandrone, and conventional stent implantation in the coronary arteries of 13 pigs (20-26Kg).

Methods: A BiodivYsioTMDD stent, was completely embedded for 5 minutes in a 5 ml solution of cis-platinum (1mg/0.5ml) and mitoxandrone (4.75mg/4.5ml). Thereafter, the stent was allowed for 5 minutes to dry ensuring no contact with any surface. Seven BiodivYsioTMDD stents were implanted to LAD and 6 to LCx. Thirteen conventional stents were placed in the other branch of the left coronary artery serving as control. Balloon to artery ratio was 1.17 ± 0.1. Maximum balloon pressure was 15 atm. At 5 weeks, the animals were sacrificed after completion of coronary angiography and morphometric studies were performed.

Results: All vessels were patent after the implantation except of one 1 case of subacute thrombosis in the control group. Restenosis was observed in one vessel of the control group. Histologically, endothelialization was similar between the two groups. The arterial middle layer was thinner in the drug delivery stent compared to the control group.

Conclusions: The results of the present study show that stent-based delivery of cis-platinum combined with mitoxandrone is feasible and reduces restenosis. These positive results encourage further clinical investigations.

871 VEGF-eluting stents reduce stent thrombosis, but not restenosis, in vivo

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Local drug delivery by stent has been shown to reduce in-stent restenosis in recent encouraging trials (e.g. ELUTES, RAVEL, TAXUS). We report the use of VEGF delivered by polymer-coated stents.

VEGF is an endothelial-cell specific mitogen. After stenting, the arterial endothelium is almost entirely denuded. This loss of endothelium contributes to the smooth muscle cell (SMC) proliferation seen in restenosis, since SMCs become exposed to mitogens in the blood. Furthermore, endothelium actively inhibits SMC hyperplasia, by producing NO and heparans. Over time, the endothelium recovers, "passivating" the stent and SMC hyperplasia is arrested.

We aimed to speed the re-endothelialisation process by delivering VEGF absorbed into the polymer coating of a stent. We also tested whether VEGF - which stimulates NO - reduces stent thrombosis. Both effects might reduce intimal hyperplasia.

Work in vitro confirmed that Cook polymer-coated stents absorbed and then gradually released VEGF. This released VEGF stimulated the growth of endothelial cells adjacent to the stent.

VEGF-loaded or control stents were then tested in a New Zealand White rabbit iliac artery model. Acute thrombosis was measured in the vessels using Indium-labelled platelet deposition. The extent of endothelialisation (using scanning electron microscopy) and subacute thrombosis was measured at 7 days. At 28 days the amount of intimal hyperplasia was determined from morphometric analysis of H&E stained, resin-embedded cross sections of stented vessels.

Acute thrombosis was less on the VEGF coated stents, but this did not achieve significant levels (P=0.2). At 7 days, thrombus formation was significantly reduced -median weight of thrombus 12.5mg (controls) v. 0mg (VEGF), p=0.014. However, no beneficial effect was seen on endothelialisation, which was minimal and unquantifiable in both groups, or intimal hyperplasia. Luminal area was 4.4±1.0mm^2 (control) v. 4.7±0.5mm^2 (VEGF), p=0.45. Neointimal area was 2.2±0.9mm^2 v 2.4±1.8mm^2 (p=0.8).

Conclusions Vascular endothelial growth factor delivery by stent in this model does not seem to alter re-endothelialisation. No beneficial results were seen on restenosis. A beneficial effect on thrombus formation early after stent implantation was seen. Such an effect, which may be mediated by NO production, would make these stents less thrombogenic than current clinically used stents.

872 The effect of local simvastatin delivery on neointimal formation in vivo after vascular injury: comparison with rapamycin

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Background: Although statins have been shown to exert anti-proliferative effects on smooth muscle cells in vitro, the previous major prospective human clinical trials failed to corroborate the beneficial effect of statin therapy on restenosis after conventional coronary balloon angioplasty. However, systemic administration for a local problem such as restenosis does not seem the most logical approach. The aim of this study was to investigate the effect of local simvastatin delivery on neointimal formation in vivo.
Methods: 15 Wister rats were randomized in the simvastatin group (SIM, n = 6), the rapamycin group (RAP, n = 6) or the control group (CON, n = 3). After angioplasty, an osmotic pump (ALZET, USA) was placed outside the injured carotid artery and then the rats were allowed to recover. The pump was filled with 50iM simvastatin in the SIM group, 50iM rapamycin in the RAP group and vehicle only in the CON group. The infusion was continued for 14 days. The sections of the injured arteries were examined in 3 rats in each group at 14 days and those of remaining 3 rats in the SIM group and the RAP group were examined at 28 days.
Results: A significant reduction of neointimal thickness was observed in the SIM group (32.0±23.5 mm, p = 0.03) and the RAP group (33.0±11.0 mm, p = 0.02) at 14 days when compared with the CON group (106.0±30.8 mm). In the SIM group, the neointimal thickness observed at 28 days (45.0±24.4 mm) was similar to that at 14 days (p = 0.53). In the RAP group, the neointimal thickness at 28 days (87.0±36.7 mm) increased compared with that at 14 days. However, this trend (p = 0.07) failed to be statistically significant. The histologic sections stained with a polyclonal antibody against von Willebrand factor demonstrated that regenerated endothelium was present in the balloon-injured areas in the SIM group at 14 days, whereas the RAP group showed incomplete re-endothelialization at 14 days.
Conclusion: The local simvastatin delivery shows sustained reduction of neointimal hyperplasia in a balloon-injury model, while it has a favorable effect on re-endothelialization. Simvastatin is a good candidate for local delivery from a drug-eluting stent.

CARDIAC COMPUTED TOMOGRAPHY: SOMETHING NEW ON THE HORIZON?

873 The MUNICH registry: "normal" distribution of coronary artery calcium measured by 4-slice computed tomography in over 2000 asymptomatic individuals

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Accurate quantification of coronary calcium, usually by means of the Agatston calcium score, is a prerequisite for assessing calcified atherosclerotic plaque burden. For this purpose, electron-beam computed tomography (EBCT) is currently being regarded as the "gold standard". Recently, four-slice (4-S)-CT has become an alternative, new modality. However, neither a standard image acquisition protocol nor the normal distribution pattern of the calcium score in asymptomatic individuals have been established for 4-S-CT. The MUNICH registry (MUltislice Normal Incidence of Coronary Health) consecutively collects these data using 4-S-CT and prospective ECG-triggering in analogy to the MESA protocol (4x2.5 mm).
Results: Calcium was detected in 990 (65%) men and 248 (48%) women (p < 0.001). Age, gender and all of the established causal risk factors (systemic hypertension, active smoking, hypercholesterolemia, diabetes but not BMI) were independently associated with the Agatston calcium score. Age and gender specific 10th, 25th, 50 th, 75 th and 90 th percentiles of the Agatston score distribution were established and will be presented. There was a good correlation to previously reported percentile values derived from studies using EBCT.
Conclusions: The current data from the MUNICH registry establish a database for the calcium scores determined by 4-S-CT and prospective ECG-triggering in apparently healthy subjects. The similarity with percentile values previously reported in EBCT-studies suggest that 4-S-CT provides useful information about the presence and extent of coronary atherosclerosis. Since the data acquisition of the current study is comparable to the method used for the MESA study currently performed in the USA, the data from the MUNICH registry will be comparable to the 4-S-CT data from the MESA-study. There was a surprisingly good agreement between the MUNICH "normal distribution" and the published EBT data.

874 Calcium score as assessed by multislice computed tomography does not predict maximal coronary artery stenosis: an in-vitro study

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Background: Electron beam computed tomography and multi-slice computed tomography (MSCT) have been shown to accurately detect coronary calcification. However, the association of MSCT detected calcium score and percent area stenosis as assessed by intravascular ultrasound (IVUS) is unknown.
Methods: 32 human coronary arteries were fixed in a flow model and perfused with saline. After setting landmarks, an automated pull back (0.5 mm/sec) with an IVUS catheter (40 MHz) was performed through all coronary arteries. Total vessel (VA) and lumen area (LA) were measured. In addition, plaque area (PA; VA-LA) and percent area stenosis [PS=(PA/VA)x100] were calculated for each vessel (n=32) and each segment (n=599). Calcifications were identified by bright dense echo and quantified by circumferential degrees (IVUS Ca; 0-360 degrees). Following IVUS, a MSCT (Somatom Plus Volume Zoom 4, Siemens) was performed for each vessel and the results were quantified using Agatston Score.
Results: In 21 coronary arteries MSCT was able to detect calcium, whereas in 11 coronaries no calcium was found. Interestingly, average PS (62.1±7.3 vs. 57.3±5.2; p=0.06) and maximal PS (73.4±7.0 vs. 74.7±10.1; p=0.33) as assessed by IVUS were not significantly different between MSCT calcium positive and negative vessels. MSCT analyses for the single segments revealed calcium in 141 segments. However, PS was significantly higher in these MSCT calcium positive compared to the calcium negative segments (66.0±9.5 vs. 59.6±9.1, p<0.01). Also, MSCT calcium score showed a close correlation with calcium identified by IVUS (r=0.83, p<0.01), but only a weak correlation with PS (r=0.30; p<0.01).
Conclusion: Although MSCT detected coronary calcification accurately it is not necessarily associated with percent area stenosis. As maximal percent area stenosis was not different between MSCT calcium positive and negative vessels, our data do not support MSCT as a reliable means for the discrimination of patients with or without significant coronary artery stenosis.

875 Impact of the heart rate on multislice computed tomography coronary angiography

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Introduction: Multislice spiral computed tomography (MSCT) has emerged as a promising non-invasive tool to assess the coronary arteries. However, due to a limited temporal resolution the technique is vulnerable to motion artifacts caused by residual cardiac motion. We evaluated the impact of the mean heart rate (HR) on the diagnostic accuracy of MSCT coronary angiography.
Methods: IV contrast-enhanced MSCT angiography (4 x 1 mm protocol, 500 ms rotation time, Siemens VolumeZoom, Forchheim, Germany) was performed in 78 patients, who were suspected of obstructive coronary artery disease. No additional beta-blocking medication was used prior to the scan. Using retrospective ECG gating, sets of slices were reconstructed at different positions within the cardiac cycle. The data set with the least motion artifacts was selected for further analysis. All coronary segments, with a diameter >2 mm and without stents (N=25), were evaluated for >50% stenosis by two investigators and compared to conventional X-ray angiography. Stratified according to average HR during the scan, patients were divided in three equally sized groups.
Results: in the group with the lowest heart rates only few motion artifacts were encountered. The segment assessability and overall sensitivity (stenotic lesions in non-assessable segments regarded as false-negative scores) were significantly better in low heart rates (P<0.01). The coronary segment assessability, diagnostic parameters and accuracy to classify patients as no-, one- or multivessel disease, are summarized in the table.

Groups	All (n=78)	I (n=26)	II (n=26)	III (n=26)
Mean heart rate	68.0 ± 12.1	55.8 ± 4.1	66.6±2.8	81.7 ± 8.8
Assessable	68%	78%	73%	54%
Sensitivity*	84%	97%	74%	67%
Specificity*	95%	96%	94%	94%
Positive PV*	67%	82%	58%	43%
Negative PV*	98%	99%	97%	97%
Overal sensitivity	63%	82%	61%	32%
Patient accuracy	56%	73%	54%	42%

*For assessable segments; PV = predictive value.

Conclusions: the diagnostic accuracy of MSCT is significantly better in patients with low heart rates. This supports the argument for routine use of beta-receptor blocking in patients with higher heart rates.MSCT diagnostic accuracy

876 Conventional risk factor analysis versus coronary calcification scanning in patients presenting in the emergency department with chest pain

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Coronary risk factor (RF) analysis has been used to risk stratify patients. We studied if a similar analysis identifies patients at high risk of coronary artery disease (CAD) presenting to the emergency department with chest pain. Prospective enrollment criteria of the 262 patients consisted of an intermediate probability of CAD, a negative or indeterminate EKG and negative cardiac markers. All patients underwent conventional cardiac testing (serial enzyme determination, stress testing, or angiography) and determination of coronary risk factors. Coronary calcification scans (CAC) were performed using a GE-Imatron 150®. The attending physician was blinded to the result. 43 patients had a positive event, defined as an MI (by enzyme determination, n=9), or conventional testing. Lipid profiles in patients with MI were drawn at least 6 weeks from the event. Results are listed in the table below:

Risk factor analysis

Variable	Odds ratio (95% CI)	p-value
Age at enrollment	1.054 (1.005 - 1.105)	0.030
Gender; female	0.504 (0.225 - 1.129)	0.10
Diabetes	3.355 (1.088 - 10.343)	0.035
BMI	1.044 (0.982 - 1.109)	0.17
LDL - cholesterol	1.000 (0.991 - 1.010)	0.95
HDL - cholesterol	0.992 (0.967 - 1.017)	0.51
Total cholesterol	1.001 (0.994 - 1.009)	0.72
Triglycerides	1.001 (0.998 - 1.004)	0.55
Hypertension	1.661 (0.792 - 3.483)	0.18
Tobacco	1.492 (0.713 - 3.124)	0.29
Family history of MI	1.733 (0.882 - 3.406)	0.11
Framingham Risk Score	1.115 (1.012 - 1.229)	0.028
Duke Score <5	12.566 (4.673 - 33.793)	<0.0001
CAC score <0	21.224 (4.967 - 90.699)	<0.0001
CAC score <10	21.483 (7.262 - 63.549)	<0.0001

CI = confidence interval, BMI = body mass index, CAC = coronary artery calcification

Conclusions: 1) Conventional RF analysis is only marginally helpful to establish the origin of chest pain. 2) The Duke score is an independent predictor. 3) CAC is the most powerful predictor of cardiac chest pain.

877 Changes in both left- and right ventricular volumes and function after passive cardiomyoplasty assessed by electron beam computed tomography

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Purpose: To demonstrate changes in both left- and right ventricular (LV, RV) volumes and function as well as LV myocardial mass after implantation of a cardiac support device (CSD, Acorn®), a preformed knitted polyester mesh-graft placed around the ventricles to prevent further dilatation in congestive heart failure.

Material and Methods: Thirteen consecutive patients (12 males, 1 female; age 59 ± 8 years) with ischemic or primary dilated cardiomyopathy underwent electron-beam CT 2 weeks before and 6 - 9 months after CSD implantation. Standardized contrast enhanced studies were performed along the short heart axis and following parameters were calculated using the slice summation method: end-diastolic and end-systolic volume (EDV, ESV), ejection fraction (EF) and myocardial mass (MM). Additionally, the forward cardiac output (CO) was measured in the aorta using the indicator dilution method.

Results: Morphologic and morphometric assessment of the heart was feasible in all patients. Significant decreases of enddiastolic and endsystolic volumes as well as an improved function were found for both left and right ventricle (table). After CSD implantation a small hyperdense thickening along the pericardium was observed in all cases, but no patient had pericardial effusion or an intracardiac thrombus.

LV and RV changes after CSD implantation

	preoperative	postoperative
LV-EDV (ml)	406 ± 134	323 ± 133 *
LV-ESV (ml)	331 ± 127	247 ± 128 *
LV-EF (%)	19.6 ± 6.3	26.2 ± 13.5 *
CO (l/min)	3.8 ± 1.0	4.5 ± 1.6 *
LV-MM (g)	314 ± 94.6	284 ± 73.5 *
RV-EDV (ml)	216 ± 100	163 ± 78.8 *
RV-ESV (ml)	156 ± 91.8	91.5 ± 75.6 *
RV-EF (%)	35.7 ± 15.7	48.9 ± 15.4 *

* significance (paired t-test; $p<0.05$) for preoperative vs. postoperative value (mean ± standard deviation)

Conclusion: Electron-beam CT measurements yields useful additional three-dimensional information on postoperative changes in both LV and RV morphology and function. These findings supplement initial reports on the safety and the efficacy of CSD implantation.

878 Multislice computed tomography contrast enhanced imaging of arterial and venous coronary artery bypass grafts

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Background: Contrast enhanced Multislice CT (MSCT) with retrospective ECG- gated image reconstruction has been shown to provide non-invasive visualization of the coronary artery lumen. We investigated the potential value of MSCT angiography in evaluation of both arterial and venous coronary artery bypass grafts.

Methods: We studied 40 symptomatic patients (31 men, 9 women, mean age 61 years, range 44-82 years) by both MSCT (SOMATOM Volume Zoom, Siemens) and conventional coronary angiography. The mean time interval between conventional angiography and MSCT was 5 days, range 2-10 days. A total of 131 grafts (40 left internal mammary artery, 5 right internal mammary artery,9 radial artery grafts and 77 venous grafts) were studied. After intravenous injection of a non ionic contrast medium the heart was scanned from level of carina within a single breath hold. The retrospective electrocardiographically gated reconstruction sources images and three dimensional reconstructed volumes were analysed by two investigators, unaware of the results of conventional angiography. The Multislice CT images of coronary bypass grafts were compared with selective coronary bypass angiography as the control.

Results: Multislice CT defined 39 of 42 arterial grafts as patent with 93% sensitivity and 100% specificity (12/12). MSCT defined patency of 29 of 31 left internal mammary artery (sensitivity 94%, specificity 100%). MSCT visualized the anastomotic site of left internal mammary artery graft in 71% of cases (22/31). 35 of 36 venous grafts were identified as patent with a sensitivity of 97% and specificity of 97%. In venous grafts 8 of 10 high grade stenoses were correctly detected by MSCT (sensitivity 80%).

Conclusions: Our preliminary results suggest that MSCT is a promising modality for non-invasive imaging of both arterial and venous coronary artery bypass grafts and will develop into a reliable clinical technique.

STRATIFICATION IN CORONARY ARTERY DISEASE: USE OF MYOCARDIAL IMAGING

879 Magnetic resonance flow mapping for non-invasive evaluation of vein grafts after percutaneous intervention

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Background: MR flow mapping is a potential non-invasive diagnostic tool for evaluation and follow-up of grafts after PCI. However, MR reference values for function in different graft types are limited and studies focusing on the feasibility of MRI to study the effect of PCI are lacking.

Methods: Fast MR flow mapping at baseline and during adenosine-induced stress was performed in 39 non-stenotic single vein grafts and 20 non-stenotic sequential vein grafts, as well as in 15 stenotic vein grafts before and 7.3±1.5 weeks after successful PCI.

Results: Reference values in single vein grafts for baseline average peak velocity (APV), stress APV and velocity reserve were 8.6±3.4 cm/s, 20.2±9.5 cm/s, and 2.4±0.8, respectively. In sequential vein grafts, significantly higher values for baseline APV (12.2±5.0 cm/s) and stress APV (27.2±10.6 cm/s) but a similar velocity reserve (2.3±0.7) were found. After PCI significant improvements in baseline APV (pre-PCI: 9.2±6.6; post-PCI: 12.9±7.9 cm/s, $P=0.008$) and stress APV (pre-PCI: 12.9±6.3; post-PCI 27.1±13.9, $P<0.001$) were demonstrated. No improvement in velocity reserve was observed, since both baseline and stress APV improved.

Conclusions: In sequential vein grafts absolute velocity and flow values are significantly higher than in single vein grafts, underscoring the need for separate functional reference values in different graft types. Velocity reserve appears not useful to discriminate between stenotic and non-stenotic grafts. Graft function significantly improved after PCI to reference values. MR flow mapping offers perspective for non-invasive follow-up of graft function and long-term monitoring after intervention.

880 MRI predicts myocardial and vascular remodelling in patients with acute revascularized myocardial infarction

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Background: Microvascular obstruction (MO) in acute myocardial infarction (MI) is associated with a higher rate of cardiovascular complications. Purpose was to determine whether quantitatively assessed infarct volumes and presence of MO determine infarct expansion and ventricular or vascular remodeling.
Methods: 23 pts with first acute MI (57±9 years; CKmax 857±707 U/l) underwent primary PTCA (n=14), or lysis (n=5) or initial conservative management (n=4) followed by elective PTCA. In addition, all pts received maximal medical treatment as defined by guidelines, and underwent invasive coronary angiography at 3 months follow-up to ensure patency of infarct related artery (IRA).Significant restenosis was defined as > 50% diameter stenosis as assessed by quantitative coronary angiography (QCA). Cardiac MRI was performed at baseline (<5 d after MI) and follow-up (1.5 T MR tomograph, ACS NT, Philips, The Netherlands). The complete heart was imaged with multiple cine short-axis views (balancedFFE-sequence, (TE/TR/flip 1.9/4.0/60)). 15min after administration of Gd-DTPA (0.02 mmol/kg) a 3-D, navigator corrected inversion-recovery sequence (5.3/3.2/15, slice thickness 5mm, PP-delay 225-250ms) covering the complete heart was used for determination of hyperenhanced (HYPER) and hypoenhanced myocardium within the hyperenhancement (MO). Left ventricular volumes/mass, volume of HYPER and MO as well as transmural extent of MI were calculated. %Infarcted volume was defined as (HYPER+MO)/total myocardial volume.
Results: At initial MRI all pts presented with a regional hyperenhancement, 10 had MO. %Infarcted volume, but not transmural extent, correlated with CK-max (r=0.86) and LVEF at follow-up (r=-0.80). In the absence of MO, LVEDV remained unchanged (137±28 vs 136±18 ml; p=ns), while LVEF increased at follow-up (41±4 vs 47±6%; p<0.05). If MO was present, LVEF did not improve (37±11 vs 37±12%; p=ns) and there was a significant increase in LVEDV (150±37 vs 168±20 ml; p<0.05). In the acute setting 7 out of 10 pts with MO had an occluded IRA and 8 had a significant restenosis at follow up (80%), whereas only 2 out of 13 pts (15%) without MO developed a significant restenosis (p<0.01).
Conclusions: Infarct volume 3 months after revascularization can be predicted using contrast enhanced MR in the acute setting. The presence of MO predicts 1)an increase of LVEDV, 2)no improvement of LVEF and 3)development of early restenosis of IRA. Maximal medical therapy prevents myocardial remodeling in pts with MI but without MO.

881 Seven-year follow-up after a normal exercise stress sestamibi study

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Rationale. The aim of this study was to evaluate the incidence and predictors of mortality and cardiac events at long term follow up after a normal exercise stress 99m-technetium sestamibi SPECT study.
Background: A normal exercise sestamibi study identifies patients with a low event rate at an intermediate term follow up. However, the longer-term outcome has not been evaluated.
Methods: Follow up was performed in 218 patients who underwent symptom limited bicycle exercise stress test in conjunction with 99m technetium sestamibi SPECT and demonstrated normal stress and resting perfusion. Endpoints were all cause mortality and hard cardiac events (cardiac death and non-fatal myocardial infarction).
Results: Mean age was 53 ± 10 years. There were 108 men and 110 women. Forty-seven patients (22%) were known to have coronary artery disease (previous coronary angioplasty or myocardial infarction). The pretest probability of coronary artery disease in the remaining patients was low in 57 and intermediate or high in 107 patients. Mean follow up duration was 7.4 ± 1.8 (maximal = 11.7) years. The minimum follow up duration (in patients without events) was 6 years. During follow up, 13 patients died of different causes (cardiac death in one patient) and 10 patients had non-fatal myocardial infarction. The annual hard cardiac event rate was 0.7% per year during the 6 years and 2% per year during the seventh and eighth year following the test. Overall mortality rate was 0.6% during the 5 years and 1.8 between the sixth and eighth years following the test. In a Cox multivariate analysis model, exercise heart rate was the only independent predictor of hard cardiac events (Chi^2 = 12, risk ration (RR) =0.95, CI 0.92-0.98). Independent predictors of all cause mortality were age (Chi^2 = 4, RR = 1.08, CI 1-1.17) and exercise heart rate (Chi^2 = 5, RR =0.97, CI 0.95-1). By using receiver operator curves, exercise heart rate <130 beats/minutes was the best cutoff that identified patients with higher event rate.
Conclusion: Patients with normal exercise 99m-technetium sestamibi SPECT have a very low mortality and cardiac event rate at a longer-term follow up. Events occur more frequently in patients with low exercise heart rate. These patients should be closely followed and may require pharmacologic stress testing subsequently, due to the possible impact of heart rate on the sensitivity of exercise stress test.

882 Long-term prognostic value of dobutamine-atropine stress ^{99m}Tc-sestamibi SPECT: a single-center experience with 8-year follow-up

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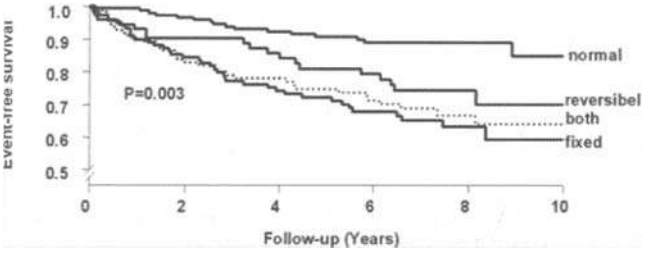
Objectives: The aim of this study was to determine the long-term prognostic value of dobutamine-atropine 99mTc-sestamibi SPECT in patients with limited exercise capacity.
Background: The prognostic value of 99mTc-sestamibi SPECT has been assessed for short- and intermediate-term follow-up. However, the long-term prognostic value is ill defined.
Methods: Clinical data and SPECT results were analyzed in 531 consecutive patients. Follow-up was successful in 528 (99.4%) patients, 55 underwent early revascularization (<3 months) and were excluded. A normal/abnormal study was considered in the absence/presence of fixed and/or reversible perfusion defects. A summed stress score (SSS) was obtained to estimate the extent and severity of perfusion defects.
Results: An abnormal scan was detected in 312 patients. During the 8±1.5 year follow-up (4.5-10.6), cardiac death occurred in 67 patients (total death 165), nonfatal infarction in 34, and late revascularization in 49. The annual event rates for cardiac death, cardiac death or infarction, and all events were 0.9%, 1.2%, and 1.5% respectively after a normal scan, and 2.7%, 3.4%, and 4.4% after an abnormal scan (P<0.05). In a multivariable Cox proportional-hazards model, not merely the presence of an abnormal scan but also the SSS provided incremental prognostic information over clinical data (P<0.0001). The hazard ratio for cardiac death was 1.09 (95% CI 1.01 to 1.18) per 1 unit increment of the SSS.



Cardiac death/infarction free survival.

Conclusions: The incremental prognostic value of dobutamine-atropine stress 99mTc-sestamibi SPECT over clinical data is maintained over an 8-year follow-up period in patients with limited exercise capacity.

883 Incremental prognostic power of the Duke treadmill score, exercise EF and SPECT imaging in high-risk patients for coronary artery disease

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Background: Non-invasive exercise testing has been shown to provide prognostic information and risk stratification mostly in patients with suspected coronary artery disease (CAD). However, the incremental contribution of the Duke treadmill score (DTS), exercise first pass radionuclide angiography (RNA-EF) and exercise perfusion SPECT imaging, has not been assessed in a high-risk population undergoing all three test modalities.
Methods: 895 patients were identified who underwent Bruce protocol exercise treadmill testing with RNA-EF and SPECT perfusion imaging as a single test between 1993 and 2000. Patients were followed for the outcomes of all-cause death, cardiovascular death (CVD), and non-fatal MI. Relative prognostic power of each test was evaluated unadjusted and adjusted for baseline characteristics using Cox proportional hazards models.
Results: During follow-up (median = 3.9 years), outcome events occurred in 163 patients. Without adjustment, each of the risk stratification modalities proved highly predictive of the combined endpoint of cardiovascular death or non-fatal MI (DTS Chi^2=13.8, p=0.0002; RNA-EF Chi^2=24.3, p=0.0001; SPECT Chi^2 = 15.5, p=0.0001). Perfusion and function imaging provided significantly more prognostic power than DTS alone. In clinically risk-adjusted models, exercise RNA-EF provided incremental prognostic information above that provided by SPECT for the end-point of CVD. Once RNA EF was known, no additional information was provided by SPECT. Conversely, exercise SPECT perfusion was a better predictor of non-fatal MI and added incremental prognostic information above that provided by RNA-EF (Incremental Chi^2 = 13.4, and 5.5, respectively, p< 0.05).
Conclusion: Exercise DTS, perfusion SPECT and exercise RNA-EF are each significant predictors of cardiovascular events in high-risk patients. SPECT imaging predicted non-fatal MI most powerfully, while RNA-EF is the strongest predictor of cardiovascular and all-cause mortality. The optimal risk stratification of high-risk patients for CAD may consist of the combined assessment of LV function and myocardial perfusion.

884 The relative prognostic value of stress nuclear perfusion versus stress echocardiography

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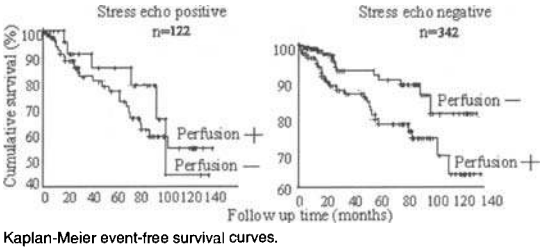
Background: Stress echocardiography and radionuclide perfusion imaging are useful imaging modalities for the diagnosis of coronary artery disease. Aim: To evaluate the long term prognostic value of the 2 imaging modalities (nuclear and echo) in patients with known or suspected coronary artery disease.
Methods: We studied 464 patients (320 males, mean age 56±10 years) who underwent on different days and in random order within one week pharmacological stress echocardiography (dobutamine; n=249, or dipyridamole; n=215) and perfusion scintigraphy (Thallium; n=122 or MIBI; n=342) with either dipyridamole (n=225) or dobutamine (n=239). All patients were followed up for 48±39 months. Patients with revascularization <12 months after testing were not included in the analysis.
Results: Seventy-two patients experienced events: 21 non fatal myocardial infarctions, 13 cardiac deaths, and 38 patients had a late (> 12 months) revascularization procedure either by PTCA (n=21) or CABG (n=17). The cumulative event free survival was 91% in patients with negative and 78% in patients with positive perfusion scintigraphy (p<0.01); 88% and 75% in patients with negative and positive stress echocardiography, respectively (p<0.01). When stress echocardiography was first incorporated in the prognostic model, scintigraphy added significant information only in patients with negative stress echo results (figure).



Kaplan-Meier event-free survival curves.

Conclusion: Stress echocardiography and perfusion scintigraphy are useful predictors, with comparable prognostic value, of late cardiac events in patients with known or suspected coronary artery disease. The incremental prognostic value of perfusion scintigraphy over stress echo is detectable in patients with negative, not with positive echo.

MYOCARDITIS: DIAGNOSTIC ASPECTS

885 Polymorphic presentation and prognostic factors in biopsy-proven myocarditis: a single centre experience in 100 cases

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The clinical spectrum of acute myocarditis (My) ranges from subtle ECG abnormalities to fulminant heart failure and sudden death. The prognostic significance of features at diagnosis (dgn) is controversial.
Methods: We studied 100 patients (pts), 62 males, aged 32 ± 19 years, mean follow-up (f-u) 30 ± 39 months. Presentation was in 18 pts with arrhythmia and/or syncope (group I), in 62 left ventricular (LV) dysfunction (group II), in 20 rest angina with abnormal troponin I (group III). 69 pts were in I/II NYHA class, 24 in III and 7 in IV; 4 pts were in atrial fibrillation, 10 had an atrioventricular block, 10 a LV bundle branch block and 14 ST-T ischemic changes. LV end-diastolic volume (LVEDV) and ejection fraction (LVEF) by 2-dimensional echocardiography (2-D echo) were 104 ± 49 ml/m^2 and 41 ± 14% respectively. Cardiac catheterization (CC) showed a mean right atrium pressure (mRAP) of 5 ± 5 mmHg and a LVEF of 43 ± 18%. Coronary angiogram was normal in all pts. Histology on endomyocardial biopsy (EMB) was of My (Dallas criteria) (91 lymphocytic, 3 polymorphic, 4 giant cell, 1 eosinophil and 1 sarcoid). Features at dgn in alive vs dead/transplanted pts as well as among groups were compared by analysis of variance; the prognostic effect of LVEF at dgn was confirmed by logistic regression in terms of odds ratio (OR) and 95% confidence intervals (CI).
Results: At f-u 61 pts were alive, 21 dead or transplanted, 18 lost; 60 pts were in NYHA I/II, 1 patient in III, with a LVEF of 51 ± 13%. Actuarial survival (Kaplan Meier) was of 69% at 3 years. Univariate predictors of death or transplantation were: NYHA II to IV (p=0.02), presentation with LV dysfunction (p=0.01), higher mRAP (10 ± 7 vs 4 ± 3 mmHg, p=0.005), lower LVEF at CC (27 ± 16 vs 47 ± 17%, p=0.004) and on 2-D echo (30 ± 10 vs 44 ± 14%, p=0.001). Group II pts had lower LVEF (p=0.0001) and greater LVEDV (p=0.0001); at f-u there were more dead/transplanted pts in Group II (38.5%, p=0.008) than in the other groups. By logistic regression, pts with LVEF at dgn between 34% and 46% had increased mortality risk (OR 10, CI 1.5-58.8, p=0.01) as well as pts with LVEF <33% (OR 16.6, CI 1.37-200,p=0.01) compared to pts with LVEF> 46%.
Conclusions: Biopsy-proven My has a high mortality rate (31% at 3 years). Clinical presentation with LV dysfunction is common; this underlines the diagnostic value of EMB in pts with LV dysfunction and normal coronary angiograms. The main independent negative predictor is the degree of reduced LVEF at dgn. The prognostic relevance of etiology (e.g. infective vs immune) remains to be clarified.

886 Endothelial dysfunction in myocardial inflammation correlates in patients' epicardial arteries, systemic arteries and coronary microcirculation

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Background: In patients with inflammatory cardiomyopathy (InfCM), immunohistological evaluation of myocardial biopsies demonstrates an inflammatory immune response in myocardium and vessels, which is associated with endothelial dysfunction of systemic arteries. Aim of this study was to investigate endothelial function (ENF)of epicardial and systemic arteries and coronary microcirculation in correlation.
Methods: ENF of epicardial arteries, coronary microcirculation and systemic arteries was tested in 51 consecutive patients with suspected myocardial inflammation. In 40 patients, InfCM was confirmed by immunohistology, 11 patients had normal myocardial biopsies. ENF of the epicardial arteries was measured during the heart catheterization, by diameter changes of the LAD in response to locally administered acetylcholine (muscarinic receptor mediated ENF (ACh3MD)) and adenosine (shear stress mediated ENF (FMDc)). ENF of the coronary microcirculation was tested via flow-wire, measuring velocity changes in the LAD during local infusion of the above vasoactive substances (CBF). ENF of the radial artery was examined by means of high resolution ultrasound, measuring flow mediated vasodilation (FMDp). ENF was compared to endothelium independent vasoreactivity to glyceroltrinitrate.
Results: Mean age of the 51 patients was 43±13 years, 29 were male, 22 female. Mean left ventricular ejection fraction was 60±15%. ENF was impaired in patients with InfCM as compared to controls. Endothelial dysfunction was demonstrated in epicardial arteries (shear stress mediated (FMDc (%) 2.90±4.83 vs. 15.05±11.08) and ACh-mediated (ACh3MD (%) -22.95 ±23.95 vs. 2.89±19.88)), in the coronary microcirculation (CBF (%) 35.62±102.07 vs. 135.81±186.9) and in systemic arteries (FMDp 3.67±2.38 vs. 6.59±4.54). The severity of endothelial dysfunction in the different vascular beds correlated: FMDc-FMDp r=0.461 (p=0.001), FMDp-ACh3MD r=0.361 (p=0.011), FMDc-ACh3MD r=0.374 (p=0.008), CBF-FMDc r=0.295 (p=0.04), CBF-ACh3MD r=0.461 (p=0.001). Endothelium independent vasodilation in patients with InfCM was only mildly impaired, as compared to controls.
Conclusions: InfCM is associated with endothelial dysfunction, which involves epicardial and systemic arteries, as well as coronary microcirculation. The extent of endothelial dysfunction in these vascular regions correlates. ENF mediated by shear stress and by muscarinic receptors is impaired. Non-invasive measurement of ENF in systemic arteries may reflect coronary endothelial function.

887 Comparison of virus serology with endomyocardial biopsy findings in patients with viral myocarditis focusing on parvovirus B19

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Purpose: Guidelines for the diagnosis of myocarditis still recommend virus serology. The present study prospectively compared results of virus serology in serum with results of viral genome detection in endomyocardial biopsies.
Method: In 92 patient with clinical suspected myocarditis at least 4 left ventricular endomyocardial biopsies were taken after invasive exclusion of coronary heart disease or valve disease by coronary angiography and left heart catheterisation. Myocardial viral genome was detected by PCR and in situ-hybridisation. Before this procedure biopsy blood samples of all patients were taken for serological analysis of infection with cardiotropic viruses (Coxsackie-, Entero-, Echo-, Adeno-, Herpes-, Influenza-, Parainfluenza-Virus as well as Parvovirus B19).
Results: In 24 of 92 patients (26%) viral genome was detected in myocardial biopsies: Entero- (n=6), Epstein-Barr- (n=3), human Herpes-6 (n=1), Coxsackie-B3-Virus (n=1) and Parvovirus B19 (n=13). In serological testing no patient revealed an acute infection with the same virus that was detected in endomyocardial biopsy. However, 23 patients showed serological signs of an infection in the past with the same virus that was detected in the myocard. In patients exhibiting myocardial virus persistence an acute myocarditis was documented once by histology and immunhistology; chronic myocarditis was observed in 15 patients and dilated cardiomyopathy in 8 cases.
Conclusion: The detection of myocardial viral genome does not correlate with the serological findings of an acute virus infection. Because of the high prevalence of these viruses in the general population virus serology does not show any benefit for the diagnostic of myocarditis. In view of the considerable costs for virus serology in serum this technique should be abandoned from the diagnostic tools in suspected myocarditis. As 54% of detected viral genome in this cohort of patients was Parvovirus B19 this virus seems to be considered as a new cardiotropic virus.

888 Enteroviral persistence and elimination are associated with the course of lymphocytic infiltration in human myocarditis

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The mechanisms responsible for viral elimination (VE) or viral persistence (VP) in enteroviral myocarditis have not been elucidated, yet.
We investigated immunohistochemically detected T-lymphocytic infiltrates (CD2+, CD3+ cells; unit: cells/high power field at 400xfold magnification) in endomyocardial biopsies (EMBs) from myocarditis patients (n=15; 4 females; age: 49±12 years; LVEF: 54±15%) with molecular biological (PCR) prove of enteroviral genome in the initial EMB. Intramyocardial infiltration and the presence of enteroviral genome were evaluated also in follow-up EMBs (2nd EMB at 6 months, 3rd EMB at 12 months after the initial presentation). At the 2nd EMB, 3 cases (20%) did not present any enteroviral genome, and at the 3rd EMB, 8 cases (53%) presented viral elimination (VE), the 3 patients showing VE at the 2nd EMB persisting negative for viral genome at the time of the 3rd EMB. Whereas T-lymphocytic infiltrates increased in VE-patients over time, T-lymphocytic infiltrates decreased significantly ($p<0.05$) in VP-patients at follow-up (MANOVA, mode: repeated measures, variable: time; table values: mean±SD). This tendency was already perceived at the 2nd EMB and pursued at the 3rd EMB (table).

	1st EMB	2nd EMB	3rd EMB
CD2-VP	5.2±6.7	4.7±4.7	2.3±2.2
CD2-VE	2.0±1.7	3.8±5.6	3.9±6.8
CD3-VP	5.2±7.4	4.9±5.3	2.3±2.6
CD3-VE	2.1±1.2	3.8±5.6	3.6±5.7

The natural course of enteroviral myocarditis significantly depends on the course of T-lymphocytic infiltration: Whereas significant increment of intramyocardial infiltration over time leads to elimination of the viral genome, decrement of lymphocytic infiltration is associated with viral persistence. Our data suggest antiviral-immunomodulatory regimens in myocarditis patients with viral persistence.

889 Significance of human parvovirus B19 in human myocarditis of the adult

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Purpose: Human Parvovirus B19 (PVB19) is an important pathogen in fetal development to childhood, e.g. causing hydrops fetalis, erythema infectiosum and myocarditis. Clinical manifestations of PVB19 infection in adults are unspecific devoid a few cases reported that showed a relationship between PVB19 and myocarditis. The aim of this study was to determine the role of human PVB19 in adult myocarditis versus specific cardiomyopathies.
Methods: A total of 86 left ventricular endomyocardial biopsies was retrieved from patients that presented with cardiac dysfunction. Myocardial specimens were analyzed by histochemistry, PCR and in-situ-hybridization for PVB19, Epstein-Barr (EBV), Enterovirus (EV) and Human Herpes Virus 6 (HHV6). Apoptosis was detected by TUNEL labeling. Enddiastolic volume (EDV), its index (EDVI) and ejection fraction (EF) were assessed by ventriculography.
Results: In 37 of 86 cases (43%), myocarditis was grouped into acute myocarditis (n=4), chronic myocarditis (n=7), with (n=11) or without (n=15) tissue defects, and into dilated cardiomyopathy (DCM, n=24), and hypertrophic CM (HCM, n=15) by histochemistry. No histopathologic abnormalities were found in 10 cases. As to myocarditis, PVB19 DNA was found in 46% of all patients (acute 50%, chronic 71%, without defect 60%, with defect 36%), EV DNA in 5%, EBV DNA in 5%, HHV6 and PVB19 DNA in 5%, EBV and PVB19 DNA in 3% positive, whereas in 35% no virus was detected by PCR (see table, figures in per cent). Comparing hemodynamic data, PVB19(+) myocarditis was associated with a lower EF than virus(-) myocarditis (39±16% vs 54±14%, p=0,012), while there were no differences in EDV or EDVI. Also, hemodynamic data and apoptosis did not correlate.

	n=86	PVB19	EV	EBV	HHV6	no virus
Myocarditis	43	46	5	5	0	35
DCM	28	4	0	0	4	92
HCM	17	13	0	0	0	87
Controlls	12	10	0	0	0	90

Conclusions: PVB19 is by far the predominant virus in adult myocarditis and mainly associated with chronic myocarditis and myocarditis without documented tissue defect. The specific pathomechanisms induced by PVB19 are still unclear and merit further consideration.

890 Active lymphocytic myocarditis: virologic and immunologic profile of responders versus non-responders to immunosuppressive therapy

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Background: The beneficial effect of immunosuppressive treatment on myocarditis is still controversial possibly because the immunologic and virologic profile of potential candidates is largely unknown.
Methods: Among 112 consecutive patients with a histological diagnosis of active lymphocytic myocarditis, 41 (29M, 12 F, mean age 42.9±13.5 years) characterized by progressive heart failure in spite of conventional supportive therapy were treated with prednisone and azathioprine for 6 months. All were re-submitted to cardiac catheterization, angiography and endomyocardial biopsy at 1 and 6 months of follow-up. 21 patients responded with prompt improvement in left ventricular ejection fraction (EF) from 25.7±4.1% to 47.1±4.4% and showed evidence of healed myocarditis at control biopsy. Conversely, 20 patients failed to respond and remained stationary (12), underwent cardiac transplantation (3) or died (5), showing a histological evolution toward dilated cardiomyopathy. We retrospectively performed a polymerase chain reaction on frozen endomyocardial tissue for the most common cardiotropic viruses and evaluation of circulating cardiac autoantibodies on pts sera.
Results: Viral genomes were present in 17 of non-responders (85%), including enterovirus (5), Epstein-Barr virus (5), adenovirus (4), both adenovirus and enterovirus (1), influenza A virus (1), parvovirus-B19 (1) and in 3 of responders, all positive for hepatitis C virus. Cardiac autoantibodies were present in 19 responders (90%) and in none of non-responders.
Conclusions: Patients with active lymphocytic myocarditis, circulating cardiac autoantibodies and no viral genome in the myocardium are most likely to benefit from immunosuppression. The beneficial effect of immunosuppression observed in HCV myocarditis suggests a relevant immunomediated component of damage.

NEW ISSUES IN HYPERTROPHIC CARDIOMYOPATHY

891 Implanteble cardioverter defibrillator utilization among device recipients with hypertrophic cardiomyopathy – The Israeli experience

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Little is known about implantable cardioverter defibrillator (ICD) discharges in recipients of devices with hypertrophic cardiomyopathy (HCM). We retrospectively analyzed ICD utilization in all ICD recipients with HCM ever implanted in Israel. Among approximately 2000 ICD implanted, 51 were high-risk patients (pts) with HCM. Thirty six (71%) were males and the mean age was 42.5 (range 13-77). The indication for the ICD implantation (imp) were:1)Secondary prevention (SP)- in 24 pts after aborted sudden cardiac death (SCD) or spontaneous sustained ventricular tachyarrhythmia (VTA). 2) Primary prevention (PP)-in 27 (53%) high-risk pts for SCD, who had at least one risk factor (family history of SCD, syncope or inducible VTA at EPS).All the ICD's had stored electrogram capability.
Results: During mean follow-up of 36.7 mos (range 3-127) [41.6 mos (range 4-127) in the SP group and 32.4 mos (range 3-110) in the PP group (p=0.24)], 16 pts (31%) had at least 1 appropriate (app) ICD discharge and 9 pts (18%) only inappropriate discharges. First app discharge occurred at a mean of 17.4 mos (range 1-73), [16.9 mos (range 1-73) in the SP group and 19.7 mos (range 14-24) in the PP group (p=0.82)], due to VTA with mean CL of 290 ms(range 200-435) diagnosed by stored electrogram in all the pts. Among the 24 SP pts 13 (54%) had at least 1 app discharge compared to only 3/27 pts (11%) among the PP pts(P=0.0037). Three pts died, 30,55, and 73 mos after the imp from non arrhythmic causes.
Conclusions: Our data support the use of ICD as secondary prevention in post event pts with HCM. However, identification of the high-risk pts candidate for primary prevention implantation remains a challenge.

892 Pregnancy related complications in women with hypertrophic cardiomyopathy

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Background: Due to lack of systematic data controversy persists as to whether or not pregnancy is well tolerated in hypertrophic cardiomyopathy (HCM).
Methods: Questionnaires were sent to 200 consecutively referred women with HCM. Clinical evaluation included history, family history, resting and ambulatory ECG, echocardiography and symptom-limited cardiopulmonary exercise testing. Obstetric notes (available in 43% of women) were also reviewed.
Results: Questionnaires were completed by 165 (82.5%) women with 127 (age 47 ± 15) having been pregnant and accounting for 271 pregnancies. Clinical data was available before pregnancy in 40 (32%) women. Eighty-seven (69%) women were referred after pregnancy (57 were diagnosed with HCM before, during or between pregnancies and 30 after pregnancy), in these data from their first clinic visit was reviewed.
Forty-three (34%) women reported cardiac symptoms before pregnancy including 10 women that were diagnosed with HCM after pregnancy. Thirty-five (28%) women reported cardiac symptoms antenatally with over 90% having been symptomatic before pregnancy. A deterioration in pre-pregnancy symptoms during pregnancy occurred in less than 10%. Of the 35 women with symptoms, 30 had further pregnancies. Symptoms reoccurred in 18 (60%) but symptomatic deterioration was not reported. Heart failure occurred post-natally in 2 women (1.6%). Nineteen (15%) women required general anaesthesia, no complications were reported. Eleven (8.7%) women known to have HCM before pregnancy received epidural anaesthesia (EA). None of these patients had significant left ventricular outflow tract obstruction (LVOTO), 2 reported dizziness and one had hypotension. No symptoms were reported in another 11 (8.7%) women that received EA that were not diagnosed with HCM before pregnancy, 3 were later found to have significant LVOTO (> 30 mmHg). Three unexplained intrauterine deaths occurred in women taking cardiac medication throughout pregnancy.
No echocardiographic or clinical feature was a useful indicator of pregnancy related complications.
Conclusions: Women with HCM tolerate pregnancy well. Medication should be stopped where possible. EA should continue to be used cautiously.

893 Cost-effectiveness analysis of screening strategies for identification of athletes with hypertrophic cardiomyopathy at risk for sudden death

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Background: We previously reported that systematic preparticipation screening by history, physical examination and 12-lead ECG successfully identifies and disqualifies young competitive athletes affected by hypertrophic cardiomyopathy (HCM) and prevents sudden death (SD) during a long term follow-up. The present study performes a cost-effectiveness analysis (cost per year of life gained) of the above preparticipation evaluation (type I screening) as compared with other two recommended cardiovascular screening modalities such as history and physical examination only (type II screening) and history, physical examination and 12-lead ECG plus echocardiography (type III screening). Methods: Among 33,735 young competitive athletes (aged 12-35 years) initially screened at the Center for Sports Medicine in Padua from 1979 to 1996 according to type I screening, only 3,016 (8.9%) were referred for echocardiography and 22 (0.07%) were actually found to be affected by HCM and disqualified from competitive sports. Accordingly, the estimated sensitivity and specificity of type I screening was 70% and 90%, respectively as compared to 20% and 95% for type II and 100% and 100% for type III screening modalities (echocardiography was deemed to be the "gold standard" for HCM diagnosis). For the purpose of the study, it was assumed that athletes with HCM who were identified and disqualified by preparticipation screening (all three screening modalities) will live the following number of years: 10% will live an additional 40 years and 90% will live an additional 20 years. The cost for performing cardiovascular evaluation was estimated at 20 euro for type I, 10 euro for type II and 100 euro for type III screening modalities.Results: The cost to initially screen 33,735 athletes and to further evaluate those 3,016 with abnormal response was 1,176,032 euro by type I screening, whereas it would have been 697,640 euro for type II and 3,373,500 euro for type III screening strategies. The total amount of life gained by type I screening was 484 years as compared with 132 years by type II and 680 years by type III. The approximate costs per year of life saved were: type I screening 2,429 euro, type II 5,285 euro and type III 4,961 euro. Conclusions: History, physical examination and 12-lead ECG was the most cost-effective preparticipation cardiovascular modality for identification of athletes with HCM at risk of SD, with an approximate cost per year of life saved of 2,429 euro.

894 Doppler tissue imaging and hypertrophic cardiomyopathy in genotyped families

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Background: In families with Hypertrophic Cardiomyopathy (HCM), the expression of the disease is highly variable and left ventricular hypertrophy (LVH) may even be absent in adults who carry the causal mutation. Pulsed Doppler Tissue Imaging (DTI) was recently proposed as a novel means for early diagnosis of HCM independently of LVH, (sensitivity: 100%, specificity: 90% for Ea <14 cm/s). We tested whether HCM consistently showed reduced myocardial velocities, irrespective of LVH.
Methods and Results: We performed 2D, Doppler and pulsed DTI (mitral annulus: MA) echocardiography in 16 adults with HCM, 7 healthy carriers (adults who carry a mutation but did not have LVH), and 7 age- and sex-matched controls. LV wall thickness, systolic and early diastolic velocities (DTI-MA) were significantly different between adults with LVH and controls ($P<0.05$ for each parameter). Between mutation-positive adults without LVH and controls, neither LV wall thickness nor systolic velocities were different. Early diastolic velocities (DTI-MA) were lower in healthy carriers than in controls (Ea: 16.3 vs 20.2 cm/s, P=0.037), but with a large overlap of individual data. Sensitivity and specificity of DTI for the diagnosis of HCM without LVH were 28% and 100% respectively.
Conclusions: In contrast with a recent report, we found that pulsed DTI at the mitral annulus level was not an accurate and sensitive method for identifying subjects who carry a mutation but have no LVH. For instance, this novel diagnostic approach should probably not be recommended for the screening and management of families with HCM.

895 Hypertrophic cardiomyopathy related deaths in an Italian tertiary center

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Background: Low mortality rates in hypertrophic cardiomyopathy (HCM) are recently reported in some community studies in comparison to higher rates as reported in referral Centers. Quantification of the risk of sudden death (SD) and death due to heart failure (HFD) is difficult to formulate.
Objectives: We calculated mortality rates in our tertiary Center and risk of SD and HFD in relation to clinical and echocardiographic variables as well as nonsustained ventricular tachycardia and atrial fibrillation.
Methods This analysis was undertaken in a population of 308 consecutively enrolled patients in a tertiary HCM center (1 to 79 years old,mean 43±18, 204 males). Twelve variables were considered: age at diagnosis, family history of sudden death (FHSD), NYHA, syncope, maximal left ventricular wall thickness(MLVWT), left ventricular end-diastolic diameter (LVEDD), left ventricular fractional shortening (LV FS),left atrium diameter (LAD), presence of gradient, atrial fibrillation (AF), nonsustained ventricular tachycardia (NSVT), therapy with Amiodarone during follow-up.
Results: HCM related-death occurred in 56 pts over the follow-up (mean of 7.16 ± 6 years, range 5 days to 28.7 years): SD in 30 pts (age 44 ± 16), HFD (of these 9 were transplanted) in 18 pts (age 47± 18) and other HCM-related death in 8 pts (age 43 ± 19). At ten years the SD-free survival rate was 89% (95% CI, 84 to 93), the HFD-free survival rate was 93% (95% CI, 90 to 97). The incidence of SD was 13.6 per 1000 person/year (95% CI, 9.2 to 19.4), the incidence of HFD was 8.2 per 1000 person/year (95% CI, 4.8 to 12.9). A significant association with HFD was identified for: NYHA functional class (I-II vs III-IV ($p<0,001$)) and the absence of outflow obstruction ($p<0,001$) at Fisher's exact test; wall thickness of 15mm or less (p=0,022) and left atrial cavity dimension (p=0,001) at chi square test for trend. The univariate association with SD was identified for LVEDD (p=0,002).Among these risk factors when together considered in the Cox model, MLVWT (cut-off value 20mm) was found to be independently and directly related to the incidence of SD (p=0.04; RR= 4.5) and LAD to the incidence of HFD ($p <0.001$;RR 3.1) and death from any cause (p=0.0054; RR 1.4)Therapy with Amiodarone during follow-up is an independently protective factor for death from any cause p=0,022;RR 0,2).
Conclusions: Among numerous variables only wall thickness greater than 20mm resulted statistically related to the risk of SD. Trigger for SD include not only extreme LVWT but factors as fibrosis and disarray.

MAGNETIC RESONANCE IMAGING IN CARDIAC ARRHYTHMIAS: A NEW ALLIANCE?

915 Non invasive classification and imaging of preexcitation sites by multichannel magnetocardiography

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Multichannel Magnetocardiography (MMCG), is a contactless method which can be used for non invasive localization and imaging of ventricular preexcitation (VPX) sites. Nevertheless so far MMCG studies of VPX patients (pts) had been done in magnetically shielded rooms only, which has limited the acceptance of this new method by clinicians, because of high cost and unfavorable location of MMCG instrumentation. After positive experience with a single channel MCG mapping system we have fostered the development and recently installed the first instrumentation for MMCG operating in an unshielded hospital environment and evaluated its reliability, with the aim to use this novel method for electroanatomical imaging also in the EP catheterization laboratory. **Method:** A 9 channels DC-SQUID MMCG system (sensitivity is 20 fT/Hz1/2) (CardioMag Imaging Inc., USA) has been used. Equivalent current dipole (ECD) and magnetic dipole (MD) models in semi-infinite space were used in the inverse calculations and 3D localization of VPX. A distributed currents model (CDI) was also used as alternative imaging procedure. Localization results were also transferred on patients MRI images. 22 WPW pts have been investigated, at least twice, to test for reproducibility, mapping 36 points from the anterior chest wall (measuring grid 20 x 20 cm). In 14 pts the second procedure was carried out on the same day, in 12 MMCG was repeated after approximately 3 months. In 6 pts, MMCG was also repeated during transesophageal atrial pacing-induced maximal VPX and/or AV reentry tachycardia. As this one was designed and ethically approved as a non invasive study only, MMCG localization of VPX was compared with that achiavable with most recent ECG algorithms. **Results:** MMCG classification of VPX was in agreement with ECG in 18/22 (81.8%). In 4/22 (18%) with conflicting results, MMCG provided a clear-cut localization in all and demonstrated complex activation patters during the delta wave in 3/4. Current density reconstruction and imaging in those cases suggested multiple activation pathways, unpredictable on the basis of ECG, in 1/4. **Conclusion:** This study demonstrates that MMCG is possible, reproducible and reliable also in our unshielded EP catheterization laboratory. As compared to ECG, MMCG classification of VPX, especially of paraseptal and multiple pathways, is more effective because MMCG provides non invasively quasi real-time 3D electroanatomical integration and imaging of the VPX sites directly on anathomical MRI images or 3D cardiac models.

916 MRI of the brain at 1.5 Tesla in patients with antibradycardia pacing: an hazardous procedure?

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Magnetic resonance imaging (MRI) is one of the most important imaging tools, particularly in the diagnosis of cerebral diseases. Most MRI scanners in the Western World operate at a field strength of 1.5 Tesla. The major concerns against their use in patients with antibradycardia pacing are due to the fact that MRI induces the heating of the pacemaker (PM) leads and pulsed magnetic fields may cause oversensing during MRI. The objective of the study was to evaluate the short-term and long-term PM function in patients with antibradycardia pacing who underwent MRI of the brain. **Methods:** A total of 57 patients with strong clinical need for MRI of the brain were scanned at 1.5 Tesla (Intera, Philips Medical Systems) with 22 patients followed up for at least 3 months yet. Patients with an intrinsic heart rate <35/min were excluded. After the PM was programmed to an asynchronous mode the MRI was performed under cardiological surveillance, continous ECG monitoring and pulse oxymetry. Radiofrequency exposure was restricted to the whole-body-averaged maximum Specific Absorption Rate (SAR) of 1.2 Watt/kg, the imaging time of each sequence to 10 min with a pause of at least 5 min between two sequences to allow cooling of the lead tips. The lead impedances, battery function, pacing and sensing thresholds were determined before, immediately after and 3 months after the MRI of the brain. **Results:** All MRI scans were performed safely in the absence of any complications. Pacing thresholds, sensing thresholds, battery function and lead impedances did not change significantly immediately after and 3 months after the MRI of the brain.
Conclusions: 1. Using appropriate strategies (programming to asynchronous mode, MRI adequate cardiac monitoring, restricted radiofrequency exposure) the MRI of the brain at 1.5 Tesla can be safely performed in carefully selected PM patients. The PM testing immediately after and 3 months after MRI did not reveal any short-term or long-term damages of the antibradycardia pacing systems or major temperature-induced injuries at the PM lead insertions. 2. Therefore the MRI of the brain should not be considered as absolute contraindication in PM patients. 3. However, due to its potential risks MRI in patients with antibradycardia pacing should only be performed in experienced centres.

917 Magnetic resonance imaging in arrhythmogenic right ventricular dysplasia: assessment of myocardial abnormalities

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Background: Arrhythmogenic right ventricular dysplasia (ARVD) has been increasingly found in patients (pts) with right ventricular (RV) arrhythmia. Although, MRI has been widely applied, diagnostic value of MRI myocardial abnormalities in evaluation of ARVD pts has not been well established. Therefore, the aim of the study was to assess diagnostic value of myocardial abnormalities in these pts and to find the best performing MRI criteria for ARVD.
Patients and Methods: The study group included 307 pts, 51.1% males (157/307), mean age 42.7±15.2 years, who were referred to the Cardiology Department for evaluation of RV arrhythmia. All patients underwent clinical examination, electrophysiologic study, echocardiography and MRI using cine and TSE T1 and T2 sequences on a Siemens Magnetom Sonata, 1.5T scanner. MRI was performed to evaluate presence of the major ARVD criteria and minor ARVD criteria. A scoring system with ranking for major and minor criteria was established. However, only 53 pts (17.6%), 64.2% males (34/53), mean age 44.2±15.4 years, had RV abnormalities on MRI. After complete examination, this group was reviewed and according to the final diagnosis, divided into the group with ARVD {group 1, 17 pts (32.1%)} and the group with other RV abnormalities {group 2, 36 pts (67.9%)}.
Results: Among major criteria, fatty replacement was present only in 3 (17.6%) pts in the group 1, ($p<0.01$). Also, there were significantly more pts with severe RV dilatation in group 1 (64.7%) than in group 2 (17.1%), $p<0.01$, and with localized RV aneurysm (group 1, 41.2%, group 2, 0%, $p<0.01$). Most minor criteria were more frequently in group 1 then in group 2: mild global RV dilatation, (22.5% vs. 34.3%, respectively, $p<0.01$), regional RV hypokinesia (76.5% vs. 41.2% respectively, $p<0.01$), dilatation of RV outflow tract (50% vs. 11.8% respectively, $p<0.01$), prominent trabeculae (82.4% vs. 37.1% respectively, $p<0.01$). The total score for the minor and the major ARVD criteria in group 1 was Median=5, and in group 2 Median=1, which was statistically significant difference, $p<0.01$. Sensitivity of this score was 65% while specificity was 94.4%.
Conclusions: The score of major and minor MRI criteria has been proved to be useful in identifying ARVD pts with high sensitivity and specificity. Although none of the criteria could be considered as pathognomonic for ARVD, MRI could obtain reliable and reproducible data on morphologic and functional abnormalities within one study, which could direct further clinical decision making in these pts.

918 Magnetic resonance imaging of pulmonary veins before and after ablation of atrial fibrillation

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Pulmonary vein (PV) isolation is a new method to eliminate the trigger for atrial fibrillation. Different mapping and ablation procedures are used to ablate pulmonary vein ostia circumferentially or partially. A severe complication is PV stenosis/occlusion during long-term follow-up. Therefore, reliable and if possible noninvasively obtained information on the anatomy and variation prior to the intervention and on PV stenosis during follow-up is required.
Of 32 patients (P) (mean age 60±7 years, mean follow-up (FU) 5.7 months (m)) with paroxysmal or persistent atrial fibrillation and PV isolation, contrast-enhanced magnetic resonance imaging (3D FFE angiography) was performed in 23 P (9 women) to investigate PV anatomy including craniocaudal diameters (Table) and in 16 P the morphology after 3 m.
17 P had normal PV anatomy. 5 P had a common origin of 2 veins (3 x right upper + right middle lobe vein, 1 x right lower + middle lobe vein, 1 x 2 left upper pulmonary veins). 3 P had 3 right PV, in 4 P the left lower PV was small. At 3-m FU, no P showed PV stenosis. One angiographically confirmed acute stenosis had returned to normal. Two other asymptomatic acute stenoses were detected after 7 days, the 3-month follow-up results are still due.

PV	Diameter (mm)
Right upper	17.3±2.2
Right lower	17.3±2.8
Left upper	17.7±2.5
Left lower	15.0±3.2

Magnetic resonance imaging is an appropriate tool to visualize the exact anatomy of pulmonary veins prior to isolation. Being a nonvasive method it is of particular value to exclude or confirm PV stenosis during follow-up.

919 Diagnosis of pulmonary vein stenosis after radiofrequency ablation by transoesophageal echocardiography and magnetic resonance imaging

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Pulmonary vein (PV) ablation using radiofrequence energy offers the potential to cure patients with refractory atrial fibrillation. However, stenosis of the treated vessels can occur. Up to now there are no clear criteria for the diagnosis of this "new desease".
Methods: We examined 52 patients (55 ± 10 years old, 40 male) 19 ± 11 months after ablation of one ore more PV for refractory atrial fibrillation with TEE (HDI 5000; ATL, USA; 5 Mhz multiplane tranducer) or angio MRI (Magnetom Sonata; Siemens, Germany; contrast medium: Gadodiamid). The definition of a significant stenosis for TEE was a Doppler peak velocity of > 110 cm/s in combination with turbulence and deformity of the flow signal. On angio MRI stenosis of PV was assessed on angio raw images and after 3D reconstruction, a decrease in PV diameter by > 50% was considered significant. MRI and TEE were studied independently and blindly.
Results: TEE was performed in 48, MRI in 42, and both procedures in 38 patients. MRI was not performed in 6 patients with pacemaker. TEE showed 13 significant stenosis and 4 occlusions. MRI demostrated 7 stenosis > 50% and 4 occlusions. TEE could measure Doppler flow in all but one of 192 PV studied. MRI was able to reveal the complet anatomy and arbitration of all PV, but in 15 of 168 PV (9%) it was difficult to assess the ostial part of the PV because of artefacts and low spatial resolution. 151 PV were studied with both procedures. Concordance with regard to TEE and MRI PV assessment was 97% (147 of 151 PV). TEE showed two significant stenosis of minor side branches which were not detected by MRI. MRI showed 5 additional stenosis < 50%. - In the whole group of patients we found 14 significant stenosis and 5 occlusions in 114 treated PV (17%). 15 of 52 patients (29%) showed at least one significant stenosis or occlusion.
Conclusions: After ablation therapy 17% of PV develop a significant stenosis. Both MRI and TEE are able to detect PV stenosis accurately. Using our criteria of a significant stenosis concordance with regard to PV assessment is 97%. MRI can visualize the complete anatomy of the PV system, but in 9% low spatial resolution and artefacts of the PV ostium makes the exclusion of a stenosis difficult.

MAGNETIC RESONANCE IMAGING IN CARDIOLOGY: ROUTINE OR STILL NEW?

921 Right ventricular remodelling after primary angioplasty for acute myocardial infarction assessed by cine magnetic resonance imaging

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Few data are available on Right ventricular (RV) remodelling after acute myocadrial infarction (AMI). Cine magnetic resonance imaging (MRI) is one of the few techniques that provide accurate imaging of the right ventricle.
Methods: We sought to study RV volumes and ejection fraction by Cine MRI 8±4 days and 3 months after successful primary angioplasty for acute myocardial infarction in 53 consecutive patients with no clincal or electrocardiograhic evidence of RV infarction.
Results: The results are reported in the table. Compared to in-hospital measurements there was a significant decrease in RV volumes ($p<0.01$) at follow-up in patients with inferior but not anterior wall infarction.

RV volumes and function

	Anterior MI (n=34) In-hospital	Inferior MI (n=19) In-hospital	Anterior MI (n=28) Follow-up	Inferior MI (n=19) Follow-up
RV EDV (ml/m²)	80±25*	98±22	83±27	87±18
RV ESV (ml/m²)	46±17	51±12	48±23	39±10
RV EF (%)	42±13	48±7	42±13*	54±10
RV/LV EDV	1±0.3*	1.2±0.2	1±0.2	1.1±0.2
Changes in RV EDV (ml/M2)			-5.3±53*	33±47

MI: myocardial infarction; RV and LV: right and left ventricular; EDV and ESV: end diastolic and systolic volumes; EF: ejection fraction. *$p<0.01$ anterior vs inferior MI.

Conclusions: Our data show evidence of reversible right ventricular remodelling early after acute inferior wall infarction despite absence of clinical or electrocardiographic evidence of RV infarction. There is no sign of right ventricular remodelling after anterior wall infarction.

922 Safety and feasibility of high-dose dobutamine-atropine stress MRI for diagnosis of myocardial ischaemia: experience in 500 consecutive patients

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Introduction: High-dose dobutamine stress MRI (DSMR) recently emerged as a new highly accurate diagnostic modality. However, prior experience with other methodologies using dobutamine infusions has shown that severe complications may be expected in 0.25-0.6% of patients (pts).
Methods: from 1997-2001, 500 consecutive pts (60±9 yrs, range 23-84; prior myocardial infarction 28%; prior percutaneous or surgical revascularization in 41% and 18%) with suspected (n=195; 39%) or known (n=305; 61%) coronary artery disease underwent DSMR (1.5 T Philips). Images were acquired at rest and during a standardized high-dose dobutamine-atropine protocol in 3 short-axis, a 4- and a 2-chamber view. A single-slice segmented turbo gradient echo technique (TR/TE/flip 5.6/1.9/25; spatial res<=1.5x2.5x8 mm; temporal res<30 ms), and from 2001 on, a balanced FFE technique (TR/TE/flip 3.0/1.5/55; spatial res<=1.7x2.7x8 mm; temporal res<42 ms) were used. Dobutamine was infused at doses of 10, 20, 30, and 40 μg.kg-1.min-1, and supplemented by atropine if needed, until >=85% of age-predicted heart rate was reached. Stress testing was discontinued when >=85% of age-predicted heart rate was reached, on patient request, termination of the protocol, or when new or worsening wall motion abnormalities, severe angina or dyspnea, decrease in systolic blood pressure (BP)>40 mmHg, arterial hypertension (>240/120 mmHg), or severe arrhythmias occurred.
Results: DSMR was successfully performed in all but 2 pts (0.4%, insufficient ECG-triggering). Heart rate increased from 67±12 to 135±18 bpm, systolic BP from 131±22 to 158±34 mmHg, and diastolic BP from 73±12 to 76±16 mmHg (p<0.0001 for all). However, target heart rate was not reached in 69 pts (14%), due to end of protocol in negative submaximal examinations in 25 pts (5%), and limiting side effects in 42 pts (9%), including severe chest pain (n=15) or dyspnea (n=4), ventricular extrasystoly (n=7), severe increase (n=6) or decrease(n=3) in BP, atrial fibrillation (AFib; n=4), nausea (n=1) or patient request (n=2).
In diagnostic examinations, other side effects included a case (0.2%) of sustained ventricular tachycardia (VT) requiring external defibrillation, 3 cases (0.6%) of non-sustained VT, 2 further cases (0.4%) of AFib, and 8 further cases (1.6%) of nausea. 194 pts (39%) showed a new or worsening wall motion abnormality, while 237 (47%) did not.
Conclusions: High-dose DSMR is safe and feasible in pts with suspected or known coronary artery disease. However, pts must be closely monitored, and resuscitation equipment and trained personnel must be available.

923 Utility of quantitative parameters for early diagnosis of right ventricular dysfunction in patients with chronic right ventricular overload

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Background: We examined quantitative parameters for early right ventricular (RV) dysfunction during pharmacological stress and the relation between the cardiac reserve and plasma neurohormones in patients with chronic RV pressure and combined pressure and volume overload.
Methods: Thirty-one patients with chronic RV pressure and/or volume overload (thirteen patients with pulmonary artery stenosis, 15 patients with corrected Tetralogy of Fallot, three patients with pulmonary hypertension)(RVSP>35 mmHg, age 27±7 years, NYHA class I and II) and ten age- and sex matched healthy volunteers were studied. The patients were divided into two groups: pressure (group 1) and pressure combined with volume overload (group 2). Valvular regurgitation of >10 ml/beat was a selection criterion for volume overload. MRI was applied both at rest and during dobutamine stress to determine RV volumes and ejection fraction (EF). Brain natriuretic peptide (BNP) was determined in all patients and controls.
Results: At baseline there were no significant differences in RV parameters between patient group 1 and controls. However, significant differences between patient group 2 and controls were found: RV stroke volume (57±17 vs 43±9ml, p<0.05), RV end diastolic volume (EDV) (113±30 vs 62±14 ml, p<0.001) and RVEF (51±8 vs 69±10%, p<0.001). During dobutamine stress there was a significant decrease of RV stroke volume in both patient groups (1: 44±8 vs 39±10ml, p<0.01 and 2: 57±17 vs 47±17ml, p<0.05) accompanied by a significant decrease in RVEDV. This was in contrast to the controls where a significant RV stroke volume increase was monitored (43±9 vs 52±12ml, p<0.01) without significant changes in RVEDV. RVEF increased significantly in the controls (69±10 vs 84±4%, p<0.001), in contrast to both patients groups where no increase was noticed after dobutamine infusion. Group 2 had significantly higher BNP than the controls and group 1(8.4±4.3 vs 2.2±1.77pmol/L, p<0.0001 and 4.2±4.9 pmol/L, p<0,04, respectively). Significant inverse correlation was found between BNP and the change in stroke volume during dobutamine infusion r=0.51; p=0.005.
Conclusion: In asymptomatic patients with chronic RV pressure and volume overload a decreased RV stroke volume is accompanied by both impaired RV filling (diastolic dysfunction) and a failure to augment RVEF (systolic dysfunction) during dobutamine stress. Adverse stress reaction and increase in BNP levels were more accentuated in patients with combined pressure and volume overload. Diminished cardiac reserve correlates with increased plasma neurohormones.

924 Diagnostic value of MRI in patients with atrial septal defect in comparison to heart catheterization and transoesophageal echocardiography

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Background: The defect diameter, shunt volume and size of right atrium (RA) and right ventricle (RV) are essential data for planning transcatheter closure of an atrial septal defect (ASD). Although, balloon sizing of the defect on heart catheterization (HC) is still mandatory, and transesophageal echocardiography (TEE) is widely used as non invasive imaging technique, magnetic resonance imaging (MRI) may play an important role in preprocedural evaluation of these patients. Therefore, we assessed the diagnostic value of MRI in the evaluation of size defect, shunt volume and RV diameters in comparison to HC and TEE.
Patients and Methods: Sixty patients, male 30% (18/60), average age 44.3±15.7 (range 15-74 years) with an ASD II were enrolled. They underwent TEE, HC and MRI (1.5T Siemens Vision® or Sonata system®). A Flash 2D cine GRE sequence (TR 60ms, TE 5ms, slice 6 mm) and a TrueFISP cine sequence (TR 32ms, TE 1.6ms, slice 5 mm) were used. On MRI Qp/Qs was calculated and compared to the HC Qp/Qs ratio. Defect size measurements of different techniques were compared. Investigators were blinded to the results of the other techniques.
Results: Qp/Qs ratio on baseline MRI examination was 1.56±0.29 (range 1.05-2.2) while on HC 1.71±0.30 (range 1.2-2.4). Correlation was statistically significant (r=0.65, p<0.01). Defect size on MRI was 15.3±7.4 mm (range 3-30 mm), on TEE 14.3±4.9 mm (range 4-24 mm), and the balloon stretched diameter on HC was 23.4±4.2 mm (range 14-32 mm). Correlation between defect size as on MRI vs TEE was (r=0.67, p<0.01), MRI vs HC (r=0.77, p<0.01), respectively. Linear regression equation for prediction the defect size on heart catheterization based on MRI is as follows (R=0.77, R2=0.59, F=38.1, p<0.01): y=14.9 + 0.6 x MRI defect size.
Conclusions: Thus, MRI proved to be an accurate diagnostic tool in pre interventional assessment of ASD patients planned to undergo transcatheter occlusion. These data indicate that MRI allows complete assessment of morphological and hemodynamic parameters in these patients without radiation and only minimal patient discomfort.

925 MRI of aortic coarctation. Pre and postoperative correlation with echocardiography, catheterization and surgery

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Objectives: Pre and postoperative MRI results were correlated in a retrospective study with echocardiography, catheterization and surgical findings.
Material and methods: 111 MRI were performed in 96 patients, separated in two groups: group I, preoperative: 49 MRI and group II, postoperative: 62 MRI: The study was conducted on a Picker 1.5 Tesla scanner and consisted of spin-echo T1 weighted sequences in all cases, cine-GE sequences in 103 cases, Gadolinium-enhanced MR angiography in 53 cases and velocity-encoded cine MRI in 40 cases (VEC-MRI). In group I, correlation was made with echocardiography (n=49), catheterization (n=14) and surgery (n=34) while in group II correlation was made with echocardiography in 51 cases.
Results: 2 MRI were nondiagnostic due to poor-quality images. Aortic coarctation was not asserted in 6 cases of group I. Other MRI correlated well with surgery for morphological measurements of the preductal aorta (r=0.93), the post ductal aortic diameter (r=0.81), the left subclavian artery involvement (r=0.88) and the presence of an associated aortic hypoplasia. Correlation was less good for measurement of the isthmic narrowing (r=0.44). Correlation of MRI and Doppler estimates of pressure gradients was possible in 20 cases with good results (r=0.69). In group II, 21 patients had a persistant pressure gradient in Doppler (> 20 mmHg). MRI was normal in 2. In 19 cases, abnormal turbulent flow was demonstrated by MRI, corresponding to recoarctation (n=5), kinking without stenosis (n=2), and persistence of a significant aortic arch hypoplasia (n=12). In 27 cases of normal echocardiography, MRI demonstrated: a large pseudoaneurysm (n=1), recoarctation (n=1), kinking without stenosis (n=2) and persistence of aortic arch hypoplasia.
Discussion: MRI provided an excellent morphologic assessment of aortic coarctation and the oblique sagittal and coronal planes seemed to be the most informative. GE-cine sequences, associated with VEC-MRI in multiple planes, allow a complementary functional dynamic evaluation of the malformation. Gadolinium-enhanced breath-hold MR angiography advantageously replaces conventional angiography. MRI is the technique of choice in the postoperative follow-up of these patients superior to echocardiography.
Conclusion: This retrospective study of aortic coarctation is the largest one published so far, and the first one with surgical correlation of MRI anatomic findings. Our results are in agreement with previous reports of the literature and provide more informations in the technique of MRI examination in aortic coarctation.

926 Aortic elasticity of the Marfan aorta: comparison between patients with and without aortic root replacement

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Objective: Aortic elasticity is related to aortic rupture behavior and may serve as an additional risk factor. Aortic elasticity can be expressed in terms of distensibility and flow wave velocity, and is decreased in Marfan patients. Aim of this study was to compare aortic elasticity assessed with magnetic resonance (MR) imaging in Marfan patients with and without an aortic root replacement.
Design and patients: Forty-two Marfan patients (mean age 33 (12) years, age range 16-55 years) with an elective aortic root replacement and 78 Marfan patients without aortic root replacement (mean age 31 (8) years, age range 18-50 years) underwent MR flow mapping at four levels (1: ascending aorta, 2: thoracic descending aorta, 3: descending aorta at the level of the diaphragm and 4: abdominal descending aorta) in the aorta. Distensibility at each level and flow wave velocity between levels were calculated.
Results: There was no significant difference in clinical characteristics between the operated and non-operated patients. Operated Marfan patients had significantly increased flow wave velocity in the aortic arch (FWV 1-2) compared to non-operated Marfan patients (5.4 (2.7) m/s vs. 4.4 (1.1) m/s, $p<0.01$). At all other levels, no significant differences in aortic elasticity between Marfan patients with and without aortic root replacement were shown. A positive correlation was found between FWV in the entire aorta and age in operated Marfan patients (r=0.69).
Conclusions: Marfan patients with aortic root replacement had higher FWV in the aortic arch, which can be attributed to more severe involvement of the cardiovascular system, older age, and/or the Dacron graft in the ascending aorta. In the descending aorta, no significant difference in elasticity between patients with and without aortic root replacement was found. These results suggest that patients after an elective aortic root replacement are not at higher risk for aortic complications in the residual aorta than non-operated patients.

COMPUTER DEMONSTRATION

937 Secure internet-based transmural heart failure registry to support interacting health care providers

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Introduction: The growing number of patients with chronic heart failure (HF) and their frequent hospital admissions create an increasing load on hospital facilities. By performing intensive monitoring the fragile equilibrium of these patients can be better controlled, e.g. by fine tuning their medication, thus preventing rapid deterioration of the patient's condition resulting in hospital admissions. Monitoring can be performed in dedicated outpatient clinics or by specialized nurses visiting them at home or performing telephone-checkups. However, this approach requires the different health care providers to have online access to accurate patient data of previous contacts. The security issues related to such a transmural information system have to be covered conscientiously. Applying state of the art encryption technology and authentication by client certificates, unauthorized access can be prevented, and information can be distributed securely over the Internet. **Methods:** To support the MAastricht Heart failure Study (MAHS) a secure web server was built that only accepts clients who can identify themselves with a certificate issued by the hospital's own Certificate Authority (CA). In the pilot phase these client certificates are stored on the user's PC but in the near future every user will obtain a hardware key containing this certificate. A secure SSL-connection is setup based on a high-grade encryption key of 128 bits. The heart failure registry is implemented as a PostgreSQL-database and interfaced to the user via web pages created by pre-hypertext processing (PHP) scripts. After patient selection the templates for data entry and retrieval are accommodated to the role of the user. Based on the class of users they belong to, they can enter, view and/or modify data. This class also determines which views are presented. Data presentation is tailored to each different health care provider. At a glance cardiologists or general practitioners can obtain an overview of e.g. all visits the patient made or received. In the future also patients will be able to enter data concerning their physical condition and basic measurements from home-monitoring devices. Based on the incoming information the automatic generation of alerts can be enabled.
Conclusion: The use of certificates in combination with data encryption facilitates a secure interactive means of information transfer between the different professions that is essential to improve the quality and availability of professional health care for the rapidly increasing number of patients.

938 CardioCard™ – A credit card-sized electronic patient record: first experiences

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Background: The CardioCard©;, a credit card-sized CD-ROM has been developed at the University Hospital of Basel to facilitate communication between the Department of Cardiology and other physicians involved in the follow-up of patients (pat). All the cardiologic data collected at the clinic (i.e. examination reports, ecg signals, etc.) are stored on the card and secured by a code word. This information system helps to improve outpatient management and to avoid redundant examinations. **Aim:** The aim of the present study was to document the first pat experiences one year after implementation of the CardioCard©; and to evaluate possibilities of improvement. **Results:** 351 of the 536 pat who received a CardioCard©; in 2001 replied to the questionnare. 55% have the card always with them, 45% keep it at home. The majority of pat consider the CardioCard©; a useful information system (74% useful versus (vs) 8% not useful vs 18% no statement). 78% would even agree to share expenses. Only 5% expressed concerns about data security. In contrast, 40% would fear insufficient data safety in case of a transmission by internet. During a mean observation time of 6.3 ± 3.1 months data were interrogated by 26% of the pat. Pat > 60 years used the card more frequently than those ≤ 60 years (39% vs 19%). Lack of equipment was the most common reason for not using the card (62%). 14% of primary care physicians obtained informations from the card. Technical problems during interrogation of data occurred in 29%, mostly due to incorrect handling (22%). **Conclusion:** The majority of pat consider the electronic patient record CardioCard©; a useful and safe information system. Despite the short observation period the card has already been used in 26% of cases. Lack of hardware, poor computer knowledge, and insufficient information concerning purpose and features of the card are essential reasons for non-use. Thus, a carefully directed instruction for the utilization of the card and better education of concerned physicians are needed to establish the CardioCard©; in the daily medical routine.

POSTER DISPLAY II

MODERATED POSTER SESSION II

P939 Increased platelet reactivity is associated with restenosis 6 months after coronary angioplasty

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Restenosis occurs in 40-50% of patients treated with PTCA. No systemic drug have convincingly reduced the rate of restenosis, except from one minor study using antibodies against platelet derived growth factor (PDGF) showing reduction in the frequency of restenosis.

The present study was undertaken to investigate possible biochemical changes, especially related to platelet function, in blood simultaneously sampled from the aortic root (AR) and the coronary sinus (CS) during PTCA in LAD.

Methods: Blood from AR and CS were drawn before, 1 and 15 minutes after PTCA in 26 patients and the results related to the presence of restenosis 6 months later as evaluated by quantitative coronary angiography. Plasma levels of PDGF and beta thromboglobulin (BTG) were analyzed with commercial methods. Platelet counts (TRC) and hematocrit (HCT) were also measured.

Results: In blood from AR (Table 1), a significant increase in the levels of PDGF was encountered 1 min after PTCA in the patients who developed restenosis after 6 months. This difference in PDGF levels between patients with and without restenosis was sustained after 15 min. The same pattern was seen in BTG levels, whereas the other variables measured were unaffected during PTCA. Significantly higher levels of TRC were observed in the restenotic group (table). No statistically significant changes in the measured variables were found in CS during PTCA.

	Restenosis (n=14)			No restenosis (n=12)		
	Pre PTCA	1 min. after	15 min. after	Pre PTCA	1 min. after	15 min. after
HCT vol %	35.8	34.3	35.5	37.7	36.6	37.0
TRC x109/l	203¶	198	207¶	167	163	164
BTG IU/ml	43	160*¶	115¶¶	45	93	72
PDGF pg/ml	481	2417*¶¶	1367¶	825	1007	715

Median values. *p<0.05 for difference from baseline; ¶p<0.05 for restenosis vs non restenosis; ¶¶ p<0.01 for restenosis vs non restenosis

Conclusion: Individuals who later presented with restenosis had a highly significant increase in the levels of PDGF and BTG in the aortic root after PTCA, and also significantly higher number of platelets. This points to a hyper reactive state of platelets in patients prone to restenosis after PTCA, and these findings may also strengthen the hypothesis that PDGF contributes to the process of restenosis.

P940 Optimal management of neonates with large ventricular septal defect and aortic coarctation

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The aim of this retrospective study is to review our experience with large ventricular septal defect (VSD) associated with aortic coarctation in neonates, in order to assess outcome and to determine the optimal surgical option.

From 1990 to 2000, 44 neonates, aged 8 ± 7 days were referred for diagnosis of aortic coarctation associated with one large VSD. Aortic arch was hypoplastic in 35 cases (79.5%). All presented with congestive heart failure, severe in 70% needing prostaglandines and mechanical ventilation. One patient died from sepsis before surgery and 43 were operated on. First surgery was performed at the age of 13.5 ± 12 days, and included: 9 complete reparative surgery (group A), 10 isolated Crafoord operation (group B) and 24 Crafoord associated with pulmonary banding (group C). Second surgery for closure of VSD was performed later in group C (9.6 ± 9 months) than in group B (2.8 ± 2 months). Overall mortality was 34%, higher in groups A (44.5%) and C (37.5%) than in group B (20%). Four patients in group C (Crafoord with banding) died before reoperation whereas none in group B (Crafoord without banding). Survival was 90% at 1 month, 83% at 6 months, 80% at 1 year and 79% at 10 years. Aortic restenosis was observed in 11 cases (25.5%), 3 days to 10 months (mean 3.3 months) after surgery. The incidence of restenosis was not different between the 3 groups; percutaneous aortic angioplasty was performed in 5 cases (2 to 8 months postCrafoord, mean 3.8 months) and surgical aortic repair in 2 cases, with no residual stenosis.

In summary, these results show that staged surgical treatment without banding lead to a lower mortality despite earlier closure of VSD. It seems to be the best surgical management for neonates with large VSD and aortic coarctation,

P941 Eustachian valve in adult patients: association with interatrial communications and cerebrovascular events: a TEE study on 306 patients

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Background: The eustachian valve (EV) is a remnant of the embryonic right valve of the sinus venosus, embryologically EV directs the oxygen-rich blood from the inferior vena cava across the patent foramen ovale and into the systemic circulation. The EV is seen in the majority of newborn infants but much less frequently in adults studied by transthoracic echocardiography. However, neither prevalence of EV in adult patients studied with TEE, nor cinical significance of EV has been studied so far.

Purpose: We dertermined wheter this embryologic remnant is associated with interatrial communications or clinical findings.

Methods: The frequency and size of the eustachian valve was studied in 306 consecutive patients undergoing TEE in search of cardiac sorce of embolism after a cryptogenic stroke and in 95 consecutive control subjects without cerebrovascular events. The prevalence of interatrial communications was studied in all 308 patients by 2D-TEE, color-Doppler and contrast echo studies.

Results: VE was present in 182 of 306 patients (prevalence 59%). The mean size was 1,1±0.5 cm, range 0.5-2,5 cm. The Eustachian valve was associated in 70% with an interatrial communication (Correlation-coefficient r = 0.63; p < 0.001). The prevalence of interatrial communications was 31% in the control group vs 61% in patients with presumed paradoxical embolism (p< 0.001). Therefore VE prevalence was significantly higher in patients with presumed paradoxical embolism 68% (143 of 211 pts) than in the control group 33%, (31 of 95 pts; p < 0.001). There was no significant difference in the size of the EV between these groups.

Conclusion: Due to its association with interatrial communication, the Eustachian valve is a frequent finding in patients with cryptogenic stroke. By directing the blood from the inferior cava to the interatrial septum, persitence of an EV may prevent spontaneous closure of PFO after birth. EV persistence increases right to left shunting across interatrial communications which enhances the chance of paradoxical embolisation.

P942 Percutaneous closure of Ostium Secundum ASD with the Helex™ septal occluder – Results of a European multicentre study

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Background: The Helex™ septal occluder is made of ultrathin ePTFE mounted on a wire frame of nitinol available in sizes between 15 and 35 mm, with 5 mm increments. It is a non self-centering device inserted via a special 9F catheter. A device/defect ratio of 1.8/1 to 2/1 is usually recommended. After deployment it assumes the form of a flat, circular, soft double disk. Delivery can be demanding but the device can be repositioned and retrieved at any time prior to release. Previous experience suggests that it represents a good alternative for the percutaneous closure of Ostium Secundum ASD and Patent Foramen Ovale.

The purpose of this study was to evaluate data collected in a European study combining multiple centres aiming at further assessing the safety and efficacy of the device for the percutaneous closure of Ostium Secundum ASD.

Methods: ASD percutaneous closure was attempted at cardiac catheterisation performed under general anaesthesia and transesophageal echo guidance. All patients (pts) in whom implantation was attempted were included in the study. They were reviewed at 1, 6 and 12 months (M) with physical examination, ECG, chest X-Rays, transthoracic echo and fluoroscopy.

Results: Implantation was attempted in 116 pts and achieved in 114 (98%). Follow-up includes 111 pts (97%). Their ages ranged from 1 to 75 (mean 21) years and weights from 8 to 102 (mean 43) Kg; 68% were female. Balloon stretched diameters ranged from 5 to 21 (mean 13) mm; 18 pts had multiple defects and 8 had septal aneurysms. Mean implant duration ranges from 61 to 939 (mean 401) days. Complete closure was noticed in 68% of the pts prior to discharge, in 80% at 6 M (n=55) and in 89% at 12 M (n=35) the remaining having trivial/small shunts. In 5 pts embolization occurred during the procedure or within 24 hrs. Percutaneous retrieval was achieved in all, followed by the insertion of a larger Helex™ in 2 and Amplatzer™ in 3. The latter are not included in the follow-up. Late wire fracture was noted in two pts, one of them having had surgical removal and ASD closure.

Conclusions: Percutaneous closure of Ostium Secundum ASDs can be safely and efficiently achieved with the Helex™ septal occluder. Its advantages include a flexible, low profile ePTFE patch with little metal. It seems especially convenient for ASDs with multiple orifices due to its non self-centring features. Residual shunts have a low incidence and tend to decrease with time.

P943 Impact of serum troponin-I elevation on long-term survival following percutaneous coronary intervention

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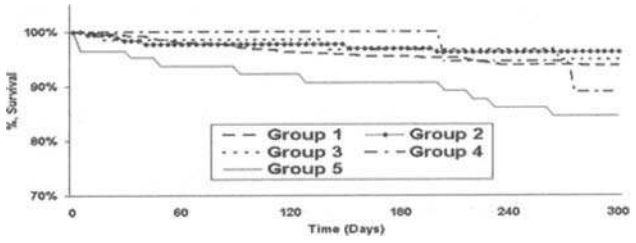
Background: Large elevations in CPK-MB following PCI are associated with decreased long-term survival. Results from studies using serum troponin-I (Tn-I) - a more sensitive biomarker of myocardial injury - have been mixed.
Objective: To estimate the impact of Tn-I elevation on survival following PCI.
Methods: We collected clinical data on consecutive subjects undergoing PCI from July 1997 to September 2000. Patients with acute ST elevation MI, non-ST elevation MI, and baseline Tn-I elevations were excluded. Tn-I levels were obtained 6 hrs and 12 to 24 hrs after PCI. Peak Tn-I levels were then used to divide subjects into 5 groups: 1) G1 - Tn-I <2.0 ng/dl (< 1 x nl); G2 - >=2.0 to <6 ng/dl; G3 - >=6 to <10 ng/dl; G4 - >=10 to <16 ng/dl; G5 - >=16 ng/dl. Follow-up data were collected at 1 mo and/or 1 yr after PCI. Using a Cox proportional hazards model, we assessed for the impact of Tn-I elevation on survival adjusting for age, gender, DM, CRI, smoking, CHF, prior MI/CABG, and procedural factors (e.g., graft PCI, stent use).
Results: 1123 subjects undergoing 1611 PCIs were analyzed with a mean follow-up of 301 days (SD, 147). Mean age was 64; 33% of subjects were women, 25% had DM, and 60% had multivessel disease. 780 (69%) subjects were in G1 based on Tn-I, 177 (16%) in G2, 68 (6%) in G3, 26 (2%) in G4, 87 (8%) in G5. After adjustment, only subjects in G5 had an increased risk of death (hazards ratio, 2.3; P=0.012). Log-rank test for equality of survival functions showed statistically significant differences between the groups (P=0.017) (Figure).



Survival After PCI based on Tn-I.

Conclusions: Tn-I elevations following PCI are common, occurring in 31% of cases. Sizeable Tn-I elevations (>8 x nl) - but not minor increases - are associated with worse survival after PCI.

P944 Fetoscopic assistance improves alignment of interventional devices during percutaneous ultrasound-guided direct fetal cardiac punctures in sheep

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Background: Difficulties with the alignment of interventional devices with the fetal cardiac outflow tracts have contributed to the unsatisfactory technical success rate of percutaneous ultrasound-guided balloon valvuloplasties in human fetuses. The purpose of this pilot study in fetal sheep was to assess the potential of a fetoscopically assisted percutaneous procedure for achieving adequate alignment with the fetal outflow tracts.
Methods: We studied a total of 4 fetal sheep between 92-102 days of gestation (term=145 days). We percutaneously entered the amniotic cavity with three trocars with an external diameter of 4 mm. Following the decision which valve ought to be passed with interventional material, fetal posturing and fixation were performed employing fetoscopic instruments. Then, a 10 F phased-array intravascular ultrasound catheter was inserted into the fetal esophagus for fetal transesophageal echocardiography. Following these steps, one or more ultrasound-guided direct punctures of the fetal heart using 16-18-gauge needles with trocar were performed. We tested adequate alignment with the right or left ventricular outflow tracts by advancing a 0.014"-guide wire across the respective semilunar valve, and recorded difficulties and complications from the procedure.
Results: Fetoscopically assisted direct ultrasound-guided cardiac punctures with optimum alignment with the outflow tracts were successfully achieved in 3 of the 4 sheep. Multimodal fetal TEE permitted imaging of the needle shafts inside the fetal heart and placement of the guide-wires across the semilunar valves in 3 of the 4 sheep. In one fetus, the needle was falsely oriented toward the right ventricular inflow tract such that wire placement across the pulmonary valve was not achieved. Because we lacked an arm (e.g. robotic arm) that permits secure fixation and precise steering of the needle inside the small fetal heart, the needle shaft dislodged in two fetuses resulting in hemopericardium, profound bradycardia, and demise. The two other fetuses were born healthy at term.
Conclusion: Fetoscopic assistance facilitates alignment of interventional devices with the fetal outflow tracts during percutaneous ultrasound-guided direct fetal cardiac punctures in sheep. This novel approach carries important potential to achieve balloon valvuloplasties in human fetuses as young as 16 weeks. Yet, further efforts, incorporating surgical robotics, need to be undertaken for securing and steering the interventional devices inside these tiny hearts.

P945 A substantial reduction in instrument size heralds clinical introduction of fetoscopic fetal cardiac interventions

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Background: Percutaneous intraamniotic insertion of 3-5 trocars that had an external diameter of 8 mm was employed for fetoscopic cardiac interventions in our early studies in sheep. Whereas the 8-mm-approach was instrumental for assessing the feasibility and for the training of various fetal cardiac interventions it might be associated with an increased risk for postoperative uterine contractions, premature rupture of membranes and premature delivery in the human. Therefore, the purpose of our experimental studies was to reduce uterine and chorioamniotic membrane injury from fetoscopic cardiac procedures by more than 75% by operating through trocars with an external diameter of only 4 mm and by modifying our technique of trocar support throughout the operations.
Methods: We studied a total of 15 fetal sheep between 68-103 days of gestation (term=145 days). We percutaneously entered the amniotic cavity with 3-4 4-mm trocars. We analyzed the success of amniotic fluid exchange, amniotic insufflation, fetal visualization, and posturing, and tried to perform various fetoscopic cardiac procedures (fetal thoracotomy, pacing, cardiac catheterization, fetal transesophageal echocardiography, overdrive stimulation) using instruments and endoscopes with diameters ranging from 1.9-3.4 mm.
Results: Percutaneous fetal access was achieved in all sheep and did not result in any fetal injury. Amniotic fluid exchange with saline followed by partial insufflation of the amniotic sac with filtered air could be achieved through the small trocars. In smaller fetuses weighing between 110–500 g the 1.9-mm endoscope was sufficient for fetal visualization and posturing. Similarly, in fetuses no larger than 1000 g the 3.4 mm endoscope was sufficient for the same purposes. The small grasping pieces of both the 2.3 and 3-mm instruments were too small for grasping the fetus. Fetal posturing was yet achieved in all instances by using the instrument shafts. The desired fetal position was maintained by T-fasteners or stay sutures that were percutaneously inserted into the amniotic cavity. Fetal thoracotomy, pacing, cardiac catheterization, fetal transesophageal echocardiography, and overdrive stimulation were all possible via the small trocars.
Conclusion: Maternal and fetal injury have now become minimal from fetoscopic fetal cardiac interventions in sheep. Fetoscopic fetal overdrive stimulation and cardiac pacing will now become clinically feasible in selected immature human fetuses with life-threatening arrhythmias refractory to conventional therapies.

P946 Percutaneous aortic valve replacement with a self-expanding stent – First animal results

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Background: Due to increasing number of elderly patients with relevant comorbidity surgical aortic valve replacement may be associate with an enormous risk. Therefore, we evaluated the feasibility of transvascular aortic valve replacement in animal experiments.
Methods: Pulmonary valves from pigs were sutured in a self-expanding stent after low-pressure fixation in glutaraldehyde solution for 72 hours. The 6 cm stent containing the biologiocal valve in its proximal part was implanted in 3 pigs (88-104 kg) by means of a 25F catheter. The catheter was introduced into the left subclavian artery. By guidance of fluoroscopy and trans-oesophageal ultrasound the valve was implanted orthotopic in the aortic position. During the implantation, the original aortic valve was pushed against the aortic wall, and the new valve was unfolded by the self expanding stent in the same moment. It was possible to replace the aortic valve in the beating heart without any complication or even relevant drops in blood pressure. Under standard hemodynamic monitoring we infused dopamine with doses of 5 μg/kg/min., 10 μg/kg/min., and 15 μg/kg/min.
Results: Cardiac output increased from 3,8 to 9,7 l/min., and the blood pressure rose from 96/54 mmHg to 138/111 mmHg respectively. The maximal peak to peak pressure gradient measured by repetitive catheter pullbacks from the left ventricle to the aorta trough the valve carrying stent increased from 0-2 mmHg at rest to 5-8 mmHg under infusion of dopamine. At the end of the acute experiments, all pigs were sacrificed by intra-coronary injection of potassium chloride after 5 hours post transvascular aortic valve replacement. The chest was opened and the left ventricle and the ascending aorta was carefully dissected. There were now signs of damage of the implanted biological valves. We did not observe any perforation of the aortic vessel wall, neither any obstruction of the coronary ostiums by the stent.
Conclusion: This study proves the feasibility of trans-vascular aortic valve replacement in the beating heart. However, further diameter reduction of the implantation-catheter-device, and additional chronic animal experiments are necessary before this technique might be an alternative for aortic valve replacement in multi-morbid patients.

P947 Treatment of pseudoaneurysms of the femoral artery by thrombin-injection: the German multicenter registry

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Background: Iatrogenic pseudoaneurysms of the femoral artery after catheter interventions can be treated by surgery or ultrasound guided compression. Thrombin injection into the aneurysm had been proposed as an alternative.
Methods: In consecutive 145 patients (age 68 ±11.3 years), a pseudoaneurysm of the femoral artery diagnosed 1 to 30 days (Median: 2 days) after catheterisation via the femoral artery was treated by local injection of thrombin solution (Thrombin Topical U.S.P. in 134 patients; Beriplast Combiset HS in 10 patients; Duett Haemostat in 1 patient). The mean diameter of the aneurysm was 2.8 ±1.1 cm.
Results: Thrombin solution (0.03 to 2.1 ml, mean 0.6 ± 0.6) was slowly injected under ultrasound guidance. In all cases, this led to immediate thrombus formation within the aneurysm. However, in 4 patients, a second thrombin injection and in 2 patients a third injection of thrombin was necessary. One patient experienced mild fever. Three patients later needed surgical removal of the resulting hematoma, one patient needed surgery for recurrent bleeding (uneventful). No other complications occurred. Follow-up duplex studies revealed no recurrences.
Conclusion: Iatrogenic pseudoaneurysms of the femoral artery can easily and effectively be treated by direct ultrasound-guided thrombin injection. In this multicenter registry the complication rate of thrombin injection was low, although the initial learnino curve was included in all centers.

P948 No impact of type of contrast medium on MACE in unselected randomized patients undergoing coronary stenting with appropriate antiplatelet therapy

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Background: The influence of type of contrast medium on ischemic complications after coronary stenting is still controversial. The aim of this study was to assess the impact of an ionic low-osmolar, and two different nonionic contrast media on major adverse cardiac events at 30 days in unselected patients undergoing coronary intervention with the use of new generation stents and appropriate antiplatelet agents.
Methods and Results: Nine-hundred and twenty eight patients treated with stent implantation were allocated to receive ioxaglate (306 patients) iopamidol (314 patients) and iopromide (308 patients). Most of these patients (55%) had an acute coronary syndrome. Glycoproteins IIb/IIIa inhibitors were used in 33% of cases. All of the patients were taking aspirin and ticlopidine for 1 month after the procedure. The primary endpoint, a composite of major adverse cardiac events at 30 days after stenting was not statistically different among the three groups (ioxaglate 3.6%; iopamidol 2.5%; iopromide 5.5%; P=0.15). Adverse drug reactions occurred more frequently in the ioxaglate patient group (4.6% vs 1.6% vs 0.6%; P=0.001). At multivariate analysis diabetes mellitus (P=0.001), intracoronary thrombus (P=0.007), multivessel CAD (0.01), and the length of the stented segment (P=0.03) were independently correlated to adverse outcome at 1 month.
Conclusions: In this unselected patients population who was treated with new generation stents and with an appropriate antiplatelet therapy no significant differences in terms of 30-day major ischemic complications were observed among patients receiving either ioxaglate, iopamidol or iopromide. These data seem to suggest that the type of contrast medium do not adversely effect stent patency.

PACING – COMPLICATIONS AND TECHNICAL ASPECTS

P949 Isolated local complications at the PM implant site are infectious complications

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Local symptoms on the PM site can be associated with infection leading to leads extraction or due to mechanical problems requiring no extraction. Patients with isolated local symptoms is a population in which a mechanical complication is often evocated, but local infection is a possible mechanism. We have try to answer at 2 questions: What is the proportion of infection in this population? And what is the optimal management of this PM complication?
Methods: In a prospective study of suspected PM infection with 224 patients included, 132 patients (45%) (68 ± 18 y.o) were referred to our institution for local symptoms on the PM site. We have studied a sub-population of patients with isolated local symptom defined as 50 patients hospitalized for local symptoms without fever, pulmonary symptoms, biologic marker of inflammation or anomalies disclosed by transesophageal echocardiography. All the implantable material (PM and leads) were systematically extracted.
Results: Only 4 patients with isolated collection of puriform liquid had negative lead cultures. In the remaining patients lead cultures were positive on the extra vascular portion. Moreover lead cultures on the intra-vascular part were positive in 31/43 (72.1%). After a follow-up of 24±17 months, recurrences of the infection occurred in 2/50 (4%) patients with isolated local symptoms. Infection recurred in 2/7 (28%) patients without complete removal of the leads.
Conclusion: Isolated local symptoms are associated with PM infection. The extravascular part of the leads but also the intravascular parts are infected. Consequently, the management of this complication, even when apparently confined to the pulse generator implantation site, should include the extraction of the entire system. A recurrence rate of 28% in patients whose lead was not completely extracted strongly supports this recommendation.

P950 Usefulness of intracardiac echography to monitor transvenous lead extraction procedures

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Transvenous lead removal is an effective technique, but possible life-treathening complications may occur, which require careful monitoring and fast diagnosis. The availability of information about 1) the condition of the intravascular part of leads, 2) the presence and extension of adhaerences to the venous wall, 3) the dimension of vegetations and their relation with the cardiac structures, may be very helpful to plane the removal procedures. Intracardiac Echography (ICE) has proven useful in the field of interventional arrhythmology and cardiac catheterization. The aim of our study was to evaluate the usefulness of ICE during transvenous lead removal procedures.

Materials and Methods: ICE was performed in 48 patients (35 men, mean age 66.3 years) who underwent removal of 90 leads (84 pacing, 6 defibrillating) due to Class I (37 pts) and Class II (12 pts) indications. The procedures were performed using the Cook Extraction kit (Cook Vascular Inc., Leechburg, PA, USA). ICE was performed using a 9 French 9 Mhz catheter, connected to Clear View Ultra EC 1003 ultrasound console (Boston Scientific Corp., S. JosE, CA, USA).

Results: the removal of leads was completed in all the patients. ICE allowed clear visualization of the leads and their adhaerences to the venous wall such as monitoring the dilation by sheaths, and the relation between the sheaths and the anatomical structures. Vegetations were observed in 66% of pts with systemic infection while Transesophageal Ecocardiography was positive in 33% of these pts. During the removal procedure, the position of the vegetations and their relation with the dilating sheaths were easily monitored. No complication related to the use of ICE was observed.

Conclusions: transvenous lead removal represents another field of application of ICE. Our experience confirmed the usefulness of this imaging technique in guiding the procedure and monitoring the possible complications.

P951 Monoclonal or polyclonal origin of pacemaker lead infection

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The notion of poly microbial infection is particularly important for anti microbial therapy and blood culture interpretation. We have looked at the leads cultures in 224 patients included in a prospective study on PM lead infection to determine if PM lead infection was due to a single or to several different microorganisms. A same species could have different clonal origins, so we have more precisely compared the DNA by pulse field gel electrophoresis (PFGE) of the coagulase negative Staphylococcus (CNS) recovered on leads in 15 patients.

Results: In 12,3% of patients no microorganism was found on the leads. An homogeneous lead cultures with the same microorganism cultured on the both extra vascular and intra vascular parts of the leads were found in 88.5% of the positive lead cultures. The extra vascular and the intra vascular parts of the leads were infected in 99.4% and 92.9%. Infection was due to Staphylococcus epidermidis and CNS in 66.0% and 29.5% respectively. Infection was poly microbial in 25.6% of cases. PFGE confirmed the monoclonal origin of species recovered on the different parts of the leads in 70.8% of the microorganism. The results of lead cultures were independent of the initial presentation (systemic infection or isolated local symptoms)

Conclusion: whatever the initial clinical presentation of PM lead infection we found the same lead culture results with infection by a CNS of both the extra vascular and intra vascular part of the leads. We can hypothesize a common mechanism of infection. In 25.6% of patients several species of microorganisms were found, and a same species could have a plolyclonal origin. This result is important for blood culture interpretation and PM lead infection management.

P952 Infected pacemaker lead extraction by means of an electrosurgical dissection sheath

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Introduction: Extraction (E) of infected pacemaker leads (L) is a difficult and dangerous procedure. It is influenced by the fixation mechanism (active/passive) and anatomic position (atrial/ventricular) of the L and the period of time the L were implanted. A new bipolar electrosurgical dissection sheath (EDS, Cook Vascular Inc., Leechburg, USA) was evaluated with regard to safety and complications.

Methods: The E was preceded by various examinations (especially a transoesophagal echocardiography TEE). After preparation and cutting of the infected L a locking stylet (LS, Liberator™, Cook Vascular Inc., Leechburg, PA USA) was introduced. A combination of an outer sheath (OS) and a 9F or 11F EDS was pushed forward over the L. Radio frequency (RF) energy (50W) was applied by means of two electrodes on the tip of the EDS if needed. A standard electrosurgical generator and an adapter were used together with the EDS. During the procedure the patient was continuously monitored by means of TEE in order to allow an instant reaction to early complications (rupture, tamponade). Cardiopulmonary bypass possibilities were always in standby. Follow up examinations were done after 24h, 3 and 30 days.

Results: 25 L (9 passive and 16 active fixation) were extracted in 14 patients. Mean time from implant to E of the L was 8,2±4,1 years. All L were removed transvenous without complications. Mean E duration was 9,5±7,8 min with an energy release for 1,8±2,0 min. Fluoroscopy time is not listed on purpose as 11 of 14 patients received a new pacemaker system during the same procedure. No complications referring to the E were observed in any patient up to 30 days after the procedure. Two patients showed minor formations of haematoma in the region of the device pocket without the need of any surgical intervention.

Conclusion: A safe use of the EDS for E of infected, transvenous L was documented. Especially the possibility of mechanical push by means of the LS, the passive mobilization of the L with the OS and the application of RF energy by means of the EDS itself are allowing to push the system forward even under difficult anatomic circumstances such as stenosis or venous caliber steps. The distinct visibility of the distal pair of electrodes is a big advantage in terms of ease of use and an increase of safety because it allows the user to align the direction of energy release away from the vessels' wall to a more central axis of the lumen. When the energy is released circularly like it is known from laser based methods the danger of creating vascular lesions seems to be much higher.

P953 The medical virtual reality lead implant simulator (VRLIS), a novel tool for education and practice of implant procedures

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Introduction: Precise lead placement is mandatory in pacing therapy. Additionally, optimization of hemodynamics reqires special lead positions in the right and left heart. The Virtual Reality Lead Implant Simulator (VRLIS) can be used to practice the positioning of leads for standard antibradycardia implants as well as left heart leads for heart failure therapy. VRLIS consits of a computer with a heart and lead model software and an interface device allowing the simulation of the handling of transvenous pacing leads at implant. The mechanical user interface mimics the lead, inserted into a vein at the implant site. The interface translates the user interaction with the lead or catheter and stylet into electrical input to the simulation software on a computer. The simulation software is based on a model of the selected lead, catheter and/or stylet and a model of the heart. Force feedback can be provided to simulate friction, entanglement or fixation of a lead. A computer display shows the ECG and the x-ray view of the respective implant situation. Different x-ray views (frontal, LAO,RAO) can be chosen, x-ray is operated by foot pedal. PSA-measurements can be taken, on-screen simulation of different stylet shapes is possible.

Method: The acceptance of VRLIS was evaluated during the meetings of the national pacing societies of Germany and Switzerland in 2001. Experienced physicians were asked to perform two virtual implants and to fill out a questionnaire. In addition, the educational effect of VRLIS was tested in community hospitals of both countries.

Results: The quality of simulation was rated by numbers from 1(poor) to 10 (excellent): lead handling 8.0 (6-9), stylet handling 8.0 (5-10), x-ray 9.4 (8-10), ECG/PSA 8.1 (3-10). All physicians trained in the community hospitals reported improvements of lead handling.

Conclusion: The VRLIS system provides a realistic impression of the lead handling during an implant simulation. VRLIS is a new, cost-effective method of accomplishing physician training/education.

P954 A new fiberoptical sensing system for the registration of changes in right ventricular contraction pattern and haemodynamics under ischaemia

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Purpose: In the electrical therapy of patients with symptomatic arrhythmia it is the objective to restore the physiologic performance as close as possible. It is desirable to achieve information about the inotropic status in addition to the electrical information of the heart. Therefore we developed a new fiberoptical sensor system for measuring heart contraction.
Method: For this study we used 6 normal hearts from adult German farm pigs. They were reperfused in an experimental set up with autologous blood for isolated biventricular working heart function. The blood volume and the preload pressures were kept constant and the new fiberoptical sensor system was placed in the left as well as in the right ventricle. The light which was emitted into the fiber was being reflected at the mirrored tip located in the heart. The contraction of the heart during each cycle caused bends of the fiber which lead to optical attenuation. All hearts were paced just above the intrinsic rate for constant heart rate during study period. The right coronary artery (RCA) was ligated proximally. The hemodynamic data were measured consistently.
Results: The sensor signal showed cyclic alterations with typical light attenuation during systolic contraction and an increase in signal amplitude during diastolic relaxation. It also showed a fast reaction to the contraction behavior and could be measured as a beat to beat change. Approximately 10 minutes after RCA occlusion the RVP has dropped by 34 ± 6%, the LVP stayed nearly constant. The pulmonary flow dropped by 38 ± 7%. At the same time the fiberoptical signal amplitude of the right ventricle dropped by 16 ± 5%, the fiberoptical signal in the left ventricle diminished only by 5 ± 4%. None of the hearts developed ventricular fibrillation directly after coronary artery occlusion but in 3 cases the rhythm converted into fibrillation 15 to 20 minutes after interruption of myocardial perfusion.
Conclusion: The fiberoptical signal is a fast reacting, beat to beat measurable, non electrical signal for registrating heart contraction. It shows a close correlation to the ventricular performance respectively to each ventricle.

P955 Correlation of device-based intra-thoracic impedance and patient fluid status during intravenous diuretic therapy in acute CHF

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Background: In patients (pts) with congestive heart failure (CHF), fluid overload may lead to hospitalization due to pulmonary congestion/edema. Monitoring of the amount of fluid retention is helpful to refine treatment and reduce hospitalizations. As fluid accumulates in the thorax, impedance is expected to decrease. Based on the preliminary results from an ongoing study, monitoring of intra-thoracic impedance (Z) using a pacemaker has been shown to provide early "warning" of impending acute CHF decompensation requiring hospitalization. During CHF hospitalization, the increase in Z correlated well with the reduction of pulmonary capillary wedge pressure (PCWP), demonstrating Z as a measure of pt's congestion. This data analysis aimed to look at the Z changes as a result of the intravenous diuretic therapy in these pts during CHF hospitalization.
Methods: Eighteen CHF pts with NYHA class III-IV (mean age 71±11 years, 14 male) received a special single chamber pacemaker (Medtronic Inc., Minneapolis, MN) with a defibrillator lead. Z was measured between the right ventricular electrodes and pacemaker can, and averaged to eliminate respiratory and cardiac influences. When the pts were hospitalized due to CHF, Z was measured every 30 min., hemodynamic intervention with PCWP measurement was performed, and the fluid status of the pts was carefully monitored. The maximum changes of Z and PCWP, as well as urine output (UO) and fluid input/output (FIO) as a result of intravenous diuretics (20-80 mg of frusemide) were calculated within the 6 hours of the therapy and averaged.
Results: Of the 16 survivors with a mean follow up of 7.9±6.1 months, 8 were hospitalized with PCWP measurement. As expected, Z increased while PCWP decreased significantly along with significant volume reductions (FIO/UO) after intravenous diuretic therapy. The increase in Z inversely correlated with FIO (r=-0.95, p=0.0003) and UO (r=-0.92, p=0.009).

PCWP Change (mmHg)	UO (ml)	FIO (ml)	Z Increase (ohms)
-3.5±4.7 (p=0.03)	-958±497*	-656±580**	6±4.5%*

*: p<0.01; **: p=0.015

Conclusion: Within 6 hours of intravenous diuretic therapy, the increase in Z closely reflects the pt's fluid balance (FIO) and diuresis. The data further validates the pacemaker-based Z as a valuable surrogate measure of fluid status in CHF pts.

P956 Peak endocardial acceleration responds as first heart sound to variation of atrioventricular delay

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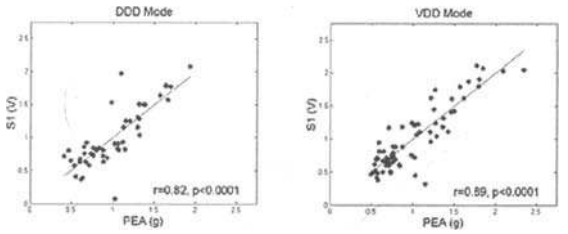
Background: PEAI is defined as the Peak Endocardial Acceleration during the isovolumic contraction phase of the cardiac cycle. Previous works showed good correlation between PEAI and LVdP/dt max, as well as its dependence on AV Delay. A similar dependence of First Heart Sound (S1) on AV Delay is also known.
Study Objective: To demonstrate the relationship between PEAI and S1 amplitudes with respect to variations in paced/sensed AV Delay.
Methods: On 7 patients (age 81±4y,3M) with high degree AV Block, simultaneous recordings from a phonocardiograph and an intracardiac accelerometer (BEST, Sorin Biomedica, Italy) were taken during execution of an AV Delay Scan (60 to 300ms, step=30ms, 60 cycles/step), in DDD (90BPM) and VDD mode. PEAI and S1 were calculated cycle-by-cycle and averaged for each AV delay. PEAI vs. S1 correlation analysis was performed after normalization to individual mean value of PEAI.
Results: Correlation for DDD mode was r=0.82, p<0.0001; for VDD mode was r=0.89, p<0.0001 (see figures)



Conclusion: This study demonstrates a high and significant correlation between PEAI and S1. S1 measurement by an implanted sensor are inherently stable and accurate.

P957 Comparison of atrial pacing from different single and dual sites: does the P-wave duration represent total atrial activation time?

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Background: The effect of dual site pacing for prevention of atrial fibrillation may be due to synchronization of right and left atrial activation. Little is known, however, about the correlation between P wave duration on the surface ECG (PWD) and endocardial total atrial activation time (TAT).
Methods: Fifteen patients without structural heart disease (9 female, 6 male, age 45±14) were studied, following ablation of supraventricular arrhythmias (AVNRT, n = 11; WPW, n = 4). Single site pacing [high right atrium (HRA), coronary sinus ostium (CSos), distal coronary sinus (CSd), high right atrial septum (Bachmann's bundle, BB)] and dual site pacing (various combinations) 10 bpm above sinus rate, and recording was performed, using standard multipolar catheters. The 65-lead body surface ECG was recorded simultaneously. Endocardial TAT was assessed offline (stimulus - last bipolar recording). The respective PWD was assessed visually after baseline correction, using the body surface root-mean-square plot and the 65-channel summary plot (stimulus - end P wave).
Results: The PWD was 121±15 ms during pacing in HRA, 108±9 ms during pacing in CSos (P<0,01), 126±14 ms during pacing in CSd (P<0,01), and 96±12 ms during pacing from BB (P<0,01). The PWD during dual site pacing (HRA+BB = 91±14 ms, HRA+CSos = 96±7 ms, HRA+CSd = 90±7 ms, BB+CSos = 91±9 ms, BB+CSd = 96±12 ms) was not significantly different as compared to pacing from BB. Pacing from BB resulted in the shortest TAT of all single sites (81±15 ms), compared to pacing in HRA (112±16 ms; P<0,01), in CSos (90±16 ms; P=0,165), and in CSd (123±17 ms; P<0,01).
Conclusions: 1) The 65-lead ECG allows for precise measurement of the PWD during pacing from all single as well as dual atrial sites; 2) surface PWD correlates with endocardial TAT; 3) BB pacing results in the shortest PWD from all single pacing sites and is comparable with dual site pacing; 4) these findings may have implications for selecting the mode and predicting the effect of preventive pacing in patients with atrial fibrillation.

P958 Comparison of long-term performance of VDD pacemakers to DDD pacemakers

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Introduction: The aim of the present study was to compare the long-term performance of VDD pacemaker(PM) implantation to DDD PM in patients(pts) with heart block and free of chronotropic incompetence.
Methods: We studied the long term performance (mean 3 years) of VDD PM in 23 pts(mean age 75±12 years, 14 male 9 female) (group I) to 23 matched pts (age 75±10 years,14 male, 9 female) with DDD PM (group II). In both study groups, the indication for implantation was 2nd or 3rd degree AV block in the absence of chronotropic incompetence. Satisfactory sensing and pacing thresholds were achieved at the implantation procedure in both groups. At a long term follow-up we defined the pacemaker performance as satisfactory when adequate atrioventricular synchrony was preserved. We use the following criteria as a marker of unsatisfactory long term performance in both study groups: 1) low P wave defined as less than double of the minimun programmable atrial sensitivity (PAS), resulting in suboptimal p wave sensing, 2) the onset of chronic atrial fibrillation (cAFib). Additional criteria suggestive of unsatisfactory performance were in group I, low sinus rate resulting in more than 20% of VVI pacing, as well as high atrial capture threshold defined as more than half the maximum atrial output in group II. Chi-square test was performed to compare the long term performance in both groups.
Results: The two study groups had a similar mean follow-up (56±18 m in group I and 62±21 m in group II). More pts in group I had unsatisfactory performance (9 pts in group I vs 2 pts in group II)($p<0.05$). In detail, the incidence of chronic atrial fibrillation was 4/23 (17.4%) in group I compared to 1/23(4.3%) in group II ($p<$NS). The incidence of low P wave, as defined previously, was 3/23(13%) to 0/23(0%) respectively ($p<$NS). Two pts in group I (8.7%) had more than 20% VVI pacing. One patient (4.3%) in group II had high atrial capture threshold.
Conclusions: According to our data DDD pacing is superior to VDD pacing in pts with high degree AV block. There is no justification for the use of VDD pacing in this group of patients. The higher incidence of atrial fibrillation in patients with VDD pacing cannot be excluded. Further studies should be carried out to elucidate this issue.

P959 Outcome and costs with an indication-optimized pacemaker selection: a prospective randomized study

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Background The selection of the optimal pacemaker system (PM) depends on the index arrythmia (sick sinus syndrome (SSS), AV block (AVB), atrial fibrillation (AF) and in the near future more and more on cost-effectiveness. Data regarding quality of pacemaker therapy versus costs are missing so far.
Methods All pts. who received a PM between 7/99 and 8/01 in the university hospital of Basel were randomized to group A (system choice according to NASPE Guidelines) or B ("optimized" system choice: AAI in isolated SSS and Wenckebach point >120/min. and not more than isolated left anterior hemiblock; VDD in AVB with chronotropic competence; otherwise DDD or VVI) or were treated open labeled (OL). Primary end points were death, heart failure (CHF), stroke (CVI), AF or angina (AP), secondary endpoints were costs. Analysis was performed on a intention-to-treat basis.
Results Out of 281 pts. receiving a PM (age 74±14y, 57% men) 94 (34%) were randomized to A and 104 (38%) to B. 83 (29%) were treated OL due to emergencies, physician's or patient's preference or concommitant studies. Regarding indications (symptoms and ecg-diagnosis) A and B were comparable as was OL (syncope 41%, dizzyness 34%, bradycardia 17%, prophylactically 10%, CHF 9% // AVB or bundle branch block 55%, SSS 28%, AVB and SSS 10%, AF 15%; all $p>0.1$). In accordance with the protocol pts with AVB in A got more DDD systems (30 vs 5) and in B more VDD (46 vs 3), with SSS in A more DDD (23 vs 10) and in B more AAI (15 vs 1), all $p<0.0001$. In binodal disease (AVB and SSS) 9 DDD and 2 VVI were implanted in each group, in AF 16 vs 11 VVI respectively ($p>0.6$). Complications did not differ between groups (hematoma (1 vs 3), pneumothorax (1 vs 1), dislocation (1 vs 3), revision (3 vs 6), $p>0.3$). Average follow-up was 351±228d. Neither mortality differed significantly (10 vs 13, log rank 0,5 (LR)) nor the combined endpoint of CHF/AP/Dyspnea (LR 0,9), nor did CVI and impaired exercise tolerance (LR 0,6). AF was even slightly increased in A (LR 0,02). Implant costs were reduced significantly in B (on average 16% or 1900 EUR/pt., ($p<0.001$).
Conclusion With our "optimized" selection of the PM-system implant costs could be reduced significantly, without a detectable impairment regarding primary end points death, heart failure, angina or exercise tolerance during 1y follow-up.

P960 Interatrial septum pacing guided by three-dimensional intracardiac echocardiography

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Background: Interatrial septum (IAS) pacing may be beneficial for the prevention of paroxysmal atrial fibrillation. Currently, the IAS pacing site is indirectly selected by fluoroscopy and P-wave analysis. The aim of the present study was to develop a novel approach for IAS pacing using intracardiac echocardiography (ICE). Methods: Cross-sectional images are acquired during a pull-back of the ICE transducer from the superior vena cava (SVC) into the inferior vena cava by an ECG- and respiration-gated technique. Both atria are then three-dimensionally (3D) reconstructed. Using an "en face" view of the IAS the desired pacing site is selected, which serves as a reference point for creating a horizontal two-dimensional (2D) template. Real-time, 2D images are then used to guide the implantation of the atrial pacing lead. After lead placement and electrical testing another 3D reconstruction is performed to verify the final lead position. Results: Thirteen patients were included in this study. IAS pacing was achieved in all patients including 6 suprafossal (SF) and 7 infrafossal (IF) lead locations all confirmed by 3D imaging approach. The mean duration of the atrial lead implantation time and fluoroscopy time were 70±48.9 min and 23.7±20.6 min, respectively. IAS pacing resulted in a significant reduction of the P-wave duration as compared to sinus rhythm (98.9±19.3 ms vs. 141.3±8.6 ms; $p<0.002$). SF pacing showed a greater reduction of the P-wave duration than IF pacing (59.4±6.6 ms vs. 30.2±13.6 ms; $p<0.004$). Conclusions: 1. Three-dimensional ICE is a feasible tool for guiding IAS pacing. 2. 3D ICE allows selection of the optimal anatomical pacing site. 3. These data suggest that the SF pacing site is preferable for pacing the IAS as it results in the shortest P-wave duration.

P961 Effect of DDDRP pacing in patients suffering from symptomatic sick sinus syndrome and paroxysmal atrial fibrillation

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Introduction Algorithms designed to prevent the occurrence of episodes of Paroxysmal AF, have become available for clinical practice. Several studies have described the high incidence of paroxysmal AF in patients with Sick Sinus Syndrome (SSS). This study will primarily focus on patients with SSS to show the efficacy of the preventive pacing algorithms available in the Vitatron DDDRP pacemakers.
Methods: This is a prospective, non-randomized, multi-center trial. Patients are eligible if they have SSS with or without pre-existing paroxysmal AF. Study procedures were based on the following steps:
1. Maturation phase of 2 weeks.
2. A monitoring phase of 1 month for monitoring the occurrence of AF and the individual onset mechanisms. The cardiac stimulator is programmed to standard dual chamber pacing with the preventive pacing algorithms OFF.
3. During the preventive pacing phase the algorithms were programmed based on the analysis of the AF diagnostics. The third and subsequent follow-ups are used to assess the efficacy of the therapy and optimise it further.
Results: From April 2000 to April 2001, 68 patients (33 m, 35 f) have been included in the study in 14 Hospitals in Spain. Mean age was 72±12 years and the pacemaker indication was SSS in 15 patients (22%) and SSS with paroxysmal AF in 53 patients (78%).
In 32 patients with pre-existing paroxysmal AF a sufficient number of follow-ups was performed in order to analyse the difference between the first follow-up and the last follow-up. The preventive pacing algorithms were programmed for each patient on an individual basis using the diagnostic features of the devices. This analysis includes 267 follow-ups, which is a mean of 4 per patient.

Endpoints	1 follow-up	2nd follow-up	Variation
AF Burden	4,9%	2%	– 61% *
N° episodes	112	62	– 60,6% *
% Atrial pacing	66%	77,6%	+15%

*$p<0,05$

Conclusions: 1. Dedicated AF diagnostics were key to adapting the optimal pacing during follow up. 2. AF prevention pacing significantly improved all AF endpoints

P962 Transvenous pacemaker implantation in children <10 kg body weight

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Background: For the majority of small children requiring permanent pacing, the epicardial approach has hitherto been preferred, due to concerns about venous access or obstruction in the long term. We report our experience with transvenous pacemaker implantation in children <10kg.
Patients: 39 children, median age 3.8 months (2 days-35 months), weight 7.5 (2.3-10)kg underwent transvenous permanent pacing (VVIR in 38, DDDR in 1). Indication for pacing was complete heart block (CHB, N=34)- congenital (21), post-surgical (11), idiopathic (2). Other indications included long QT syndrome (3), sinus node disease (2).
Methods and Results: Percutaneous transvenous access was obtained for the subclavian vein for lead introduction. Lead characteristics were as follows: 24 steroid-eluting leads and 16 non-steroid leads; 19 active fixation leads and 21 passive fixation; 13 unipolar and 27 bipolar leads. Generator location was abdominal (9), subpectoral (7) or pre-pectoral (23). In 2 patients, wound closure problems were encountered; there were no other procedural complications. Two children with post-surgical CHB died 7 days and 3 weeks post-implantation respectively, due to heart failure and septicemia, despite appropriate pacemaker therapy.
Follow-up: Over a median follow-up of 3.8 years (3 months-14.8 years) 4 patients underwent upgrading to DDDR pacing, which was successful in 3, and failed in one due to intractable AF induced by introduction of the atrial lead. Lead extraction was attempted 11 times in 9 patients and succeeded 10 times. The subclavian vein was completely thrombosed in 3; in one of them no further pacemaker therapy was performed and was well tolerated; one received a transvenous system via the same subclavian vein, and the 3rd patient received an epicardial system. In 1 patient a redundant atrial loop of a ventricular lead was adherent, and the lead was abandoned; a new transvenous lead was implanted via the cephalic vein. Other late complications included infective endocarditis of the lead (N=1, 9 months post-implant) requiring removal of the system, and pacemaker pocket infection (N=1, 19 months post-implant). Nine patients underwent 11 ventricular lead advancements, without any problems. Thirteen generators were electively replaced in 10 patients, without problems.
Conclusions: Transvenous permanent pacing is feasible and effective in children <10 kg, with a small risk of venous occlusion. There is a need to develop smaller diameter leads to avoid this.

P963 Validation of dual chamber pacemaker diagnostic data with the help of dual channel stored electrograms

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Device pacemaker diagnostic counters have been documented to include a substantial amount of false-positive or false-negative data. Aim of this multicenter study was to validate pacemaker diagnostic data using stored intracardiac electrograms (EGM) with marker annotations.
Methods: The study includes 351 pts (191 male, age 71 ± 10 y) with a dual chamber pacemaker (Pulsar Max II 1280 and Discovery II 1284, Guidant Inc.) implanted for standard indications. The devices were programmed at predischarge to store 5 dual chamber EGMs with a duration of 8 s each, including marker annotation and 4 s of onset-recording. EGM triggers have been set to: atrial tachycardia (AT), ventricular tachycardia (VT), sudden bradycardia response (SBR) and pacemaker mediated tachycardia (PMT). At the 3 month visit the EGMs were interrogated and analysed. They were classified as "confirmed" if the EGM validated the trigger, and as "false-positive" if the EGM showed an event being different from the trigger.
Results: A total of 1003 EGMs was analysed. Triggers were AT in 640 (64%), VT in 76 (8%), SBR in 105 (10%) and PMT in 178 EGMs (18%). 4 EGMs were triggered by magnet application. The trigger event was confirmed by the EGM in 618 episodes (62%). EGMs confirmed 62% of AT episodes, 18% of VT episodes, 100% of SBR episodes and 54% of PMT episodes. In 385 episodes (38%) the EGMs revealed a false-positive event. This was due to far-field sensing in 39%, noise and myopotential sensing in 26%, sinus tachycardias in 21%, double counting in 9%, exit block in 4% and undersensing in 1%.
Conclusion: This large scale study of pacemaker stored dual chamber electrograms proves their value in validating diagnostic counter data. With the exception of the sudden bradycardia response trigger, all other triggers included a considerable amount of false-positive episodes. These false-positive EGMs provided important information with the potential to optimize device programming.

P964 Benefit of the autocapture function in increasing pacemaker longevity in patients wuth a DDDR pacemaker

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Aim of the study: To evaluate, in a series of patients implanted with a DDDR pacemaker, the effect of ventricular Autocapture (AC) function on longevity of a dual-chamber device.
Methods: 114 patients were implanted with a DDDR pacemaker (St. Jude Medical Affinity, Entity) with Membrane E 1450T and EX 1470T ventricular leads. The ventricular pulse width was randomized at 0.3ms or 0.4ms at predischarge, with a cross-over every 4 weeks; AC was programmed On and ventricular threshold recordings were collected in order to calculate the battery current consumption and the projected device longevity. Current drain with AC was compared with a standard setting at discharge (3,5V/0,4 ms) and with a conventional low output setting (2,5V/0,5 ms).
Results: As shown in Table 1, a significant difference was found in projected longevity comparing different output settings. AC function allowed a prolongation of more than 1 year in the expected life of a DDDR pacemaker in comparison with projections of programming at 2.5Vx0.5 ms. Ventricular capture thresholds higher than 2,5V and 1,5V were observed in 9/114 (8%) and 24/114 (21%) pts, respectively. According to these findings, programming of a fixed 2,5V output setting would potentially result in loss of capture in 8% of pts and in lack of ventricular capture safety margin in 21% of the pts.

Table 1: Expected longevity (months)

A = 2.5V × 0.5 ms V = AC × 0.3 ms	A = 2.5V × 0.5 ms V = AC × 0.4 ms	A, V = 2.5V × 0.5 ms	A, V = 3.5V × 0.5 ms
130±6†,‡	128±8*,**	115±6	83±6

† $p < 0.001$ vs A, V = 2.5V × 0.5 ms; ‡ $p < 0.001$ vs A, V = 3.5V × 0.4 ms
*$p < 0.001$ vs A, V = 2.5V × 0.5 ms; **$p < 0.001$ vs A, V = 3.5V × 0.4 ms

Conclusions: By using AC for venticular stimulation, a significant prolongation in pacemaker longevity may be predicted, thus leading to a more favorable cost-effectiveness. The projected improvement in longevity is significant even in comparison to conventional low output pacing which, moreover, may not guarantee in all the patients maintenance of appropriate safety margins for ventricular capture.

P965 Automatic adjustment of pacing output in the clinical setting

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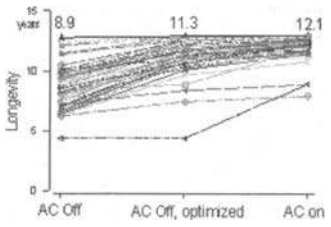
Background and aim: AutoCapture (AC) is a programmable feature which allows the recognition of cardiac evoked response for the automatic adjustment of pacing output. Although AC reduces safely the current drainage, some authors argued the longevity benefit of such a system is overstated. This study aims to estimate the longevity extension which can be obtained, in the clinical routine, by turning the AC on, when compared to factory and optimized output programming.
Methods: We selected 83 consecutive patients who had had implanted St Jude's Affinity pacemakers for at least 6 months before. Eight patients died or were lost and, in other 9 subjects, the AC could not be turned on due to lead issues. In the remaining 66 patients (33 DDDR), current drainage and estimated longevity were compared in 3 situations: I. AC on; II. AC off, optimized programming (100-150% voltage threshold); III. AC off, factory output (3.5 V). An estimate of the number of backup pulses in 24h with the AC on was obtained by Holter monitoring. The number of atrial and ventricular paced beats occurred since the last telemetric evaluation (mean: 137 days) was retrieved using the programmer.



Pacemaker longevity.

Results: The current drainage (I = 11.3 ± 2.3 mA) was reduced by optimized programming (II = 8.7 ± 1.8 mA) and, mainly, with AC on (III = 8.0 ± 0.9 mA, $p < 0,01$). Five patients had large variations (> 1V) of the AC threshold. Estimated longevity was significantly extended by AC when compared to factory (21.6 ± 10.5%) and optimized programming (7.2 ± 5.6%, $p < 0.01$).
Conclusion: Reprogramming the pacemaker output significantly enhanced its estimated longevity; AC adjusting added a moderate extension over manual reprogramming, associated with increased safety in patients with large ventricular threshold variations.

P966 Clinical evaluation of a new algorithm for closed loop stimulation

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Background: Closed Loop Stimulation (CLS), a physiologic algorithm to drive rate responsivity based on variations of intracardiac impedance signal, is triggered, up to now, by paced ventricular beats only. Recently it was developed an enhanced CLS algorithm (ECLS) that is driven by both sensed and paced ventricular beats.
Aim of this study was to validate the safety of ECLS algorithm and to compare its effectiveness with that of the standard one (SCLS) presently in use.
Methods: in 10 pts (9m; mean age 69±7 yrs), all implanted with a pacemaker model INOS2+ CLS (Biotronik, Germany), SCLS and ECLS were evaluated in a randomized and crossed over sequence at 15 and 30 days from discharge. During each control an ambulatory exercise [walking level (WL), upstairs (WU) and downstairs (WD)], mental stress and postural tests were performed. In addition, a 24-h Holter recording (Unylizer, Biotronik) was retrieved to evaluate heart rates (HR) during daily activity.
Results are shown as SCLS vs. ECLS mean data. HR increase: 23 ± 7.4% vs 28.9 ± 15.6% during WL, 45.2 ± 13.5% vs 37.9 ± 16.6% during WU, 9.2 ± 8.7% vs 23.3 ± 10.4% during WD. Time to maximum HR: 60 ± 42 vs 83 ± 49 sec during WL, 79 ± 33 vs 67 ± 45 sec during WU, 30 ± 21 vs 37 ± 12 sec during WD. P was not significative for all groups of data.
In all pts, the response of both algorithms was appropriate during all test procedures, but the proper rate response was achieved with the 93.5% of ventricular sensing in ECLS vs. the 0.7% only in SCLS ($p<0.001$). Postural changes and mental stress influenced HR by few bpm with both algorithms (p=ns). During Holter recordings ECLS showed a prompt, safe and effective rate-response suitable to patient activities. Daily ventricular pacing with ECLS was significantly lower than with SCLS (25.7% vs. 98.4%, $p<0.001$).
Conclusions: Notwithstanding the limited number of pts, data demonstrates that the enhanced CLS algorithm is safe, effective and well tolerated as the standard one. The ECLS allows to pace the ventricle only when necessary, preserving the natural ventricular activation pattern and reducing battery consumption.

P967 Closed loop stimulation and quality of life: objective and subjective results

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Introduction: The Inos2+ CLS adjusts the pacing rate accordingly to the myocardial contractility variations. It enables the cardiovascular regulatory centers to coordinate correctly the heart rate in every kind of physiological stress, improving the patient's quality of life.
Aim: To compare the subjective and objective clinical results, in DDD-CLS and DDD modes, in patient (P) with Inos2+ CLS and sinus sick syndrome.
Material and Method: Prospective and randomized (2 months after implant) study; crossover (3 months in each pacing mode), single-blind. Subjective evaluation (Quality of life - Karolinska). Objective evaluation (atrial and ventricular arrhythmias incidence by 24h Holter, in each study phase). Results: 42 P (31 chronotropically incompetent). 67% male. All P with Chagas disease and NYHA I-II.
Results:

Parameter	Result	value (t Student)
symptoms of cardiovascular disease	DDD-CLS > DDD	$p < 0.001$
physical activity and sleep	DDD-CLS > DDD	$p < 0.01$
emotional function	DDD-CLS > DDD	$p < 0.05$
cognitive skills	DDD-CLS > DDD	$p < 0.001$
sociability	DDD-CLS = DDD	NS
preferred pacing mode	DDD-CLS	$p < 0.01$ (Mann-Whitney)

Discussion: 24h Holter showed a significantly lower rate of atrial arrhythmias in P with DDD-CLS.
Conclusion: The CLS have the potential to increase the tolerance to physical activities in P chronotropically incompetent and hence improve several aspects of quality of life. This pacing mode can also be considered, an option when handling P with associated atrial arrhythmias.

P968 Vasovagal syncope and CLS pacing: preliminary results of the "INVASY" study

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Aim of the INVASY Study is to investigate whether DDD-Closed Loop Stimulation (CLS), which is sensitive to changes in myocardial contractility, can prevent malignant vasovagal syncopal recurrence (VSR) and, by consequence, it may improve the Quality of Life (QOL) in these pts.
At present 28 pts (17 m, age range 31-76yrs) were enrolled in the study and implanted with an INOS2 CLS pacemaker (Biotronik, Germany). All complied the inclusion criteria: >2 VSRs reported in the last year before implant (mean 5.4), Head-up Tilt Test (HUTT) induced syncope with hypotension and bradycardia or asystolia, cause of syncope not related to cardiac or neural pathologies. At discharge 9/28 pts were randomized in back up DDI (@40bpm) pacing mode to verify the placebo effect of pacing.
After a mean F-U time of 10.9 months: 6/9 pts paced in DDI mode had two VSRs (confirmed by HUTT) before the end of the one year F-U and were reprogrammed in DDD-CLS mode. The remaining 3/9 pts had one VSR each and are still in F-U. Of the 19 pts programmed in DDD-CLS: 9 completed the F-U without VSR (3 remained positive to HUTT); 10 are still in F-U, but none reported VSRs (5 are still positive to HUTT, 3 reported occasional symptoms of pre-syncope not followed by lost of consciousness). QOL significantly improved in all pts paced in DDD-CLS.
In conclusion, the results achieved in this early phase of the INVASY Study seems to confirm the preventive effects of DDD-CLS pacing in malignant vasovagal syncopes as previously showed by some preliminary studies.

P969 Increased morbidity related to pacemaker implantation in patients receiving chronic oral anticoagulation

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The incidence of perioperative severe adverse events (SAE) related to the management of oral anticoagulation (OA) in patients (pts) undergoing pacemaker implantation is scarcely documented. We retrospectively quantified and characterized SAEs in a case-control study between 01-1998 and 12-2000 in 114 pts with OA, mechanical valve (MV) 33%, atrial fibrillation (AF) 67%, matched with 114 control pts for age, gender, number of leads, year of implantation and type of venous access. SAE was defined as any unwanted and unexpected clinical event leading to death, reoperation or prolonging hospital stay. Procedure relatedness was defined from patients files by 3 investigators. OA was suspended 5 days before admission and heparin was substituted until 5 hours prior to surgery then resumed 5.7 ± 5.1 hours later at the discretion of the operator. In all pts, surgery was undertaken with INR and aPTT below 1.2 and 45 s respectively.
Results: Overall, SAEs occurred in 25 OA pts (22%) vs 10 control pts (9%) ($p<0.01$, RR 2.5, CI 1.3-5). Procedure-related SAEs occurred in 23 OA pts (20%) vs 8 control pts (7%) ($p<0.01$, RR 2.9, CI 1.3-6.1). These SAEs were non fatal, thrombotic SAEs were absent, bleeding and hematomas accounted for 19 SAEs in OA pts (16%) and 2 SAEs in control pts (2%) (p=0.0001, RR 9.5, CI 2.3-39.9). The sole independent variable identifying OA pts at risk for hemorrhagic SAE was the presence of MV ($p<0.05$). When restricting the analysis to the 38 MV pts and their 38 matched controls, the relative risk of hemorrhagic SAE was 11 (CI 1.5-81, $p<0.01$) with hospital stay prolonged by 9.9 days ($p<0.001$). CONCLUSIONS: OA pts are at increased risk of SAE after pacemaker implantation, the vast majority of these SAEs are hemorrhagic. Pts with MV prosthesis are at higher risk than pts with AF. Further studies are needed to define the optimal management of anticoagulant drugs in this setting.±

P970 Analysis of invasively measured pulse pressure amplitudes to optimize the av-delay in biv paced patients. Comparison with an echo and electrocardiogram method

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Background: Optimization of the atrio-ventricular delay (AVD) is a major hemodynamic factor of biventricular (BIV) pacing therapy for cardiac resynchronization. The aim of the study was to compare an intraoperative invasive method (PP-a) to determine the optimal AVD with an echocardiographic (ECHO-a) and a surface 12-channel ECG analysis (ECG-a).
Methods: The invasive blood pressure (PP) was intraoperativly monitored during BIV pacemaker implantation in 25 patients through the femoral artery. Raising AVD, beginning from 60ms to a loss of capture, were tested in 20ms intervals. The time of stimulation was 1 min preceded by a similar
intrinsic period. Accordingly to an obvious increase of the PP-amplitude, the optimal AVD was semiquantitatively determined (PP-a method). ECHO-a was performed by standard pulse doppler measurements of the mitral valve inflow from the beginning of left ventricular activation (onset QRS) to the end of E-wave (Ritter method). ECG-a was measured by the Koglek method, which uses the isovolumetric contraction time (ISVC) from the end of the p-wave to the peak of the QRS complex. The optimal AVD is the difference between programmed AVD plus 100ms and the ISVC.
Results: The mean PP-a AVD was 116 ± 21ms. In comparison the ECHO-a AVD and the ECG-a AVD was 113 ± 36ms and 117 ± 31ms. There was no significant difference between these analyzing procedures. Between PP-a and ECHO-a AVD there was a good statistical correlation (R^2 = 0,68). ECHO-a AVD vs. ECG-a AVD and PP-a AVD vs. ECG-a AVD showed less correlation (R^2 = 0,32 and 0,3).
Conclusions: The optimal AVD is simply determined intraoperatively by semiquantitative invasive measurement of the PP-amplitudes, if a raise of 10% is detectable. There is a good correlation to the echocardiographic AVD analysis, which should be additively used in patients with a hemodynamic low response.

CATHETER ABLATION – VENTRICULAR TACHYCARDIA

P971 Delineation of areas with abnormal electrograms prior to ablation of ventricular tachycardia using a three-dimensional real-time position management system

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Background: Fractionated electrograms represent sites of abnormal conduction patterns which might be target sites for radiofrequency catheter ablation (RFCA) of ventricular tachycardia (VT). In this study, we used a 3D real-time position management system (RPM) to delineate areas of fractionated electrograms.
Methods: Pts (n= 8, 6 male, 55±20yr) with ventricular tachycardia referred for RFCA were studied. A M-mode of the left ventricle was made to estimate the left ventricular end-diastolic diameter (LVEDD). RFCA of VT was guided by the RPM system. This system uses ultra-sound ranging techniques to determine the position of the ablation catheter relative to 2 reference catheters which are positioned into the right atrium and right ventricle. The length and width of the area from which fragmented electrograms were recorded were measured. Within this area, selection of target sites for RFCA was based on localization of early fragmented signals and concealed entrainment. Successful ablation was defined as non-inducibilty of the clinical VT after termination during ablation.
Results: Etiology of the VT: myocardial infarction (n=5), arrhythmogenic right ventricular dysplasia (n=1) and idiopathic (n=2). The mean LVEDD was 5.5 ± 1 cm and the area delineated in these pts was 13± 8 cm.2 In pts with a right sided VT, target sites for RFCA were located just beneath the tricuspid valve and in the RV outflow tract. Ablation was successful in 75%. In 2 pts with post-myocardial infarction VT (lateral infarction), it was not possible to terminate the VT. The area with abnormal electrograms in these patients was 8 and 10 cm.2
Conclusion: Accurate delineation of areas with abnormal electrograms prior to VT ablation with the RPM system facilitates RFCA of VT.

P972 The use of pacemapping to identify sites for ablation in patients with post myocardial infarction ventricular tachycardia

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Background Defining the sites for ablation in patients with haemodynamically unstable post myocardial infarction ventricular tachycardia (VT) requires the majority of the mapping to be performed in sinus rhythm. This study systematically evaluated multisite pacemapping in identifying sites for ablation.
Methods 10 Patients referred for catheter ablation of haemodynamically tolerated post infarction VT were enrolled and underwent study using Carto electroanatomical mapping. At each site used in construction of the baseline anatomical map, a stimulation threshold was determined by constant cycle length pacing whilst the stimulus voltage was reduced from 10 mv until the failure to capture occurred. A threshold map was created off line using the electroanatomic map as a template. The VT circuit was subsequently identified during VT by conventional means using entrainment mapping, early activation, the presence of diastolic potentials and fragmented electrograms. Radiofrequency ablation was performed and sites at which VT terminated were identified.
Results 10 patients were enrolled and decremental voltage pacemapping performed from a mean of 63 sites (range 50-73). Overall the correlation between threshold and voltage was high.Correlation coefficient r=-0.55. In the border zones between normal myocardium and dense scar, zones with significant variation between threshold and voltage were identified: 17 type A zones - with low voltages and normal thresholds and 12 type B zones - with significant variations in threshold at adjacent sites. In addition a total of 72 sites (6-10 per patient) were identified at which the S-QRS lengthened by more than 10% with decremental stimulus voltage. 86% of type A and 87% of type B zones with sites that exhibited lengthening S-QRS were located in the critical VT isthmus.
Conclusions
Pacemapping looking at stimulation threshold and S-QRS duration can identify the critical VT isthmus. This finding will assist the sinus rhythm mapping of haemodynamically unstable VT.

P973 Catheter ablation of pleomorphic ventricular tachycardia in post myocardial infarction: new goals with individual linear ablation strategies

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Radiofrequency catheter ablation (CA) of ischemic ventricular tachycardia (VT) is done in most patients (pts).after implantation of cardioverter/defibrillators (ICD). New ablation strategies with modification of the arrhythmogenic substrate using individually targeted linear lesions aim at complete noninducibility with an impact on the overall future therapy of these pts.
In 38 pts (age, 63 ± 8 years) with remote myocardial infarction (ejection fraction, 30 ± 15%) and pleomorphic and/or incessant (n=23) VT, electroanatomic (Carto) mapping using activation as well as voltage maps was performed. According to the analysis of the voltage map in addition to a limited activation map, individually designed linear lesions were placed aiming at a modification of the substrate with ablation of all potential so-called central common pathways. These strategies included connection of different scar areas, transsection of scar areas carrying surviving muscle strands, and/or connection of arrhythmogenic areas to anatomic boundaries. After CA, 26 pts (68%, group I) were completely noninducible, in 6 pts (16%, group II) nonclinical VTs were inducible after ablation, and in 6 pts (16%, group III) the target VTs could not be ablated successfully. Pts. with primary successful ablation had significantly more often incessant VT but did not differ from pts. of the other groups in respect to age, ejection fraction or medication. Successfully ablated VTs were slower compared to partially successfully ablated VTs (cl 430 ± 80ms vs, 360 ± 90ms; $p<0,05$). During the follow-up period of 126 months, 4 pts of group I (16,7%) experienced further episodes of VT, 4 pts of group II (67%) and 1 pt of group III (17%), respectively, but frequency of VT episodes and concomitant ICD discharges was significantly reduced. Within the this period, 4 pts died (2 pts. of group I and III each), all of whom had an ICD, one pt. of group I died of incessant VT.
A detailed analysis of the arrhythmogenic substrate using voltage mapping as well as limited activation mapping with subsequent placement of strategic linear lesions can result in a complete noninducibility in 75% of pts with previously pleomorphic and/or incessant VT.

P974 Radiofrequency ablation for incessant ventricular tachycardia or arrhythmic storm in patients with implantable defibrillator

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Despite Implantable defibrillator (ICD) is an effective therapy for ventricular tachycardia (VT), some patients (pts) need aditional measures to control their arrhythmic episodes. The purpose of the study was to analyze the proportion of pts requiring VT radiofrequency ablation during follow up, after ICD implant, and to describe the characteristics and results of the ablation procedure.

Methods and Results: Among 403 consecutive pts that received an ICD, fourteen (3.5%) required a VT ablation procedure after a mean of 12±13 months (from 15 days to 45 months). the precipitating event was incessant VT in 10 pts and arrhythmic storm in 4 pts. There were 12 men and 2 women, mean age was 63±16 years (range: 15-78). Nine had coronary artery disease, 4 had idiopathic dilated cardiomyopathy and 1 patient had arrhythmogenic right ventricular dysplasia (a 15 year old girl). Mean ejection fraction was 26±7% (range: 17 to 40%). VT was hemodinamically tolerated (mean cycle length 422±100 ms from 280 to 620 ms). The mean duration of the procedure was 84±27 min and number of pulses was 14±10. Two patients underwent an epicardial approach (one because intraventricular thrombus and a second due to failure of the endocardial procedure during the same session). The RF ablation was effective in 11 pts (79%). Three of them required a second procedure. In 3 pts the ablation was unsuccessful. One was submitted to heart transplant, one pt died in incessant VT. Another patient underwent successful DC ablation. The only complication was a fatal ischemic stroke. Pts were discharged on amiodarone (12 pts) or sotalol (1 pt). During a mean follow up of 11±16 months only 2 pts had an episode of VT treated successfully by the device. Two pts died during follow up because of heart failure (3 and 6 months after ablation).

Conclusions: In ICD recipients, the development of incessant VT or arrhythmic storm requiring VT ablation was very uncommon. The arrhythmic episode was successfully controlled in the majority of pts with endocardial or epicardial radiofrequency ablation, or DC shock ablation. Mortality during follow up was related to heart failure but not to arrhythmia recurrence.

P975 Identification and three-dimensional display of scar related areas of block in patients with postinfarct ventricular tachycardias during sinus rhythm

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Isolated potentials (IP) during sinus rhythm (SR)indicate the presence of an area of fixed block. Areas of fixed block might form one of the boundaries of a reentry circuit in postinfarct patients with ventricular tachycardia (VT). The 3 dimensional display of such a contiguous area with IPs during SR and its relation to the reentry circuit of postinfarct VT has not been described.

Methods: In 10 patients (pts)(all men, age 69±7yrs EF: 0.25±0.13) with recurrent postinfarct VT, the left ventricle (LV) was mapped with respect to activation time (AT) and bipolar electrogram (EGM) amplitude during SR (CARTO, Biosense, Inc.). Ten clinically relevant VTs were targeted in the 10 pts. Low-voltage segments (LVS)(amplitude <1mV) were distinguished from higher voltage segments (amplitude >1mV). AT during SR was color-coded and superimposed onto the geometrical reconstruction of the LV using a fixed reference point. IPs were defined as potentials separated from the ventricular EGM by an isoelectric line. The AT of sites with IPs was defined at the offset of the isoelectric line separating the ventricular EGM from the IP. Contiguous isochronal segments with IPs during SR were marked. Their relationship to the reentry circuit of postinfarct VT was then assessed during VT by entrainment mapping. Results: In all of the pts contiguous areas with isolated potentials could be identified. Multiple isochronal segments of IPs were identified within a single low-amplitude area in 7/10 pts. In 3/10 pts the isochronal IP area formed a border with another anatomically fixed barrier (in 2 pts with the mitral valve annulus and in 1 pt with a surgical scar after aneurysmectomy). Concealed entrainment could be demonstrated adjacent to the contiguous isochronal segments of IPs originating from the latest ventricular activation during SR in all pts. RF ablation of 8/10 targeted VTs was successful.

Conclusion: IP isochrones identify areas of fixed block during SR. The IP isochrones associated with the latest ventricular AT during SR identify a protected area that borders part of the reentry circuit of postinfarct VT.

P976 Selection of target sites for ablation of ventricular tachycardia using non-contact ventricular waveforms

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Introduction Target sites for ablation of ventricular tachycardia (VT) are crucial pathways of slow conduction, which can be identified by the presence of prolonged, low voltage electrograms. Mapping for identification of successful target sites can be performed during sinus rhythm (SR), pacing (P) and VT. This study evaluated differences between non-contact unipolar ventricular waveforms (VW) recorded from normal and infarcted myocardium.

Methods VW were recorded from pts (n=10, age 55±12 yr.) who underwent an ablation of drug-refractory post-infarction VT (CL 230±25 ms), using a non-contact mapping system (Ensite). VW's were off-line obtained from a rectangular area (n=32, ±12X15 mm, inter-electrode distance 3-4 mm) from both normal and infarcted (ablation area) myocardium during SR, P and VT. Duration and morphology of VW's between different sites and rhythms were compared.

Results Duration of VW's recorded from the infarcted area was longer than from normal myocardium during SR, P and VT ($p<0.01$)*. The morphology of VW's recorded during VT was complexer than during SR and P ($p<0.01$)**. Selection of target sites was performed during VT and successful ablation was achieved in 80%. All target sites were characterized by fragmented electrograms.

Ventricular Waveforms

	Duration (ms)		Morphology	
	+	−	+	−
SR	162/11	183/8*	biphasic (100%)	biphasic(42%), low voltage (58%) **
P	157/9	173/10*	biphasic (100%)	biphasic (26%), low voltage (74%) **
VT	105/7	142/7*	biphasic (100%)	biphasic (9.7%), low voltage (65%), fragmented (25.3%) **

+ = normal myocardium, − =infarcted myocardium, */**P<0.01

Conclusion Duration and morphology of VW's are suitable parameters to distinguish normal from infarcted myocardium. In normal myocardium, there was an uniform morphology during SR, P and VT, indicating tight electrical coupling. In infarcted myocardium, morphology of VW's varied with different rhythms, indicating non-uniform anisotropy of infarcted tissue. The duration of VW's during SR and P can be used to identify the arrhythmogenic substrate and the morphology of VW's during VT can be used for the selection of target sites for ablation of VT.

P977 Radiofrequency catheter ablation of ventricular tachycardia late after myocardial infarction: short- and long-term outcome

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Introduction: Radiofrequency catheter ablation (RFCA) of ventricular tachycardia (VT) is potentially curative. The aim of this study was to evaluate both short- and long-term outcome in a consecutive series of pts with ischemic heart disease.

Methods: From 1997 until 2001, 89 consecutive pts (70 male, 66±10 yrs, 5 pts with incessant VT) underwent RFCA for drug refractory VT due to previous MI. Thirty pts (34%) had a ventricular aneurysm. LV ejection fraction was 29±11%.

Results: In total, 187 VT morphologies were induced and targeted for ablation (2.1±1.3 VT/pt). Majority of the VT's originated from the LV (149, 95%). The procedure was successful in 79% (non-inducibility of VT after RFCA). Procedure-related complications were observed in 7 pts (8%). Two pts died (2.2%, both with incessant VT) due to hemodynamic deterioration despite a successful ablation procedure. Two pts (2.2%) suffered from an ischemic stroke and 3 pts (3.4%) had a complete heart block. Before discharge, an ICD implantation was performed in 25 pts (29%) because of a non- successful procedure and/or hemodynamically non-tolerable VT/Ventricular Fibrillation (VF). During follow-up (19±20 months), a recurrence occurred in 24% of all pts. Significantly more recurrences were observed in the non-successfully ablated pts than in the successfully ablated pts (53% vs 16%, $p<0.001$). Eleven pts with an ICD (44%) experienced ICD therapy for VT/VF (25±65 therapies/pt, range 0-257). Eight pts died during follow-up because of heart failure, whereas 2 pts died a non cardiac death (sepsis:1, malignancy:1). No patients died suddenly.

Conclusion: RFCA of VT is successful and relatively safe. The recurrence rate of the successfully ablated pts is promising. During follow-up no pts died due to VT/VF.

P978 Isthmus characteristics of reentrant ventricular tachycardia after myocardial infarction

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Background: The reentrant mechanism of post-infarct ventricular tachycardia (VT) has been documented by per-surgical mapping analysis, but little is known about post-infarct VT circuits and characteristics of their related protected isthmus using 3D catheter mapping systems.
Methods and Results: A 3D electroanatomic mapping was performed in 21 consecutive patients with well-tolerated post-infarct sustained VT. In total, 33 VTs (mean cycle length = 432±74ms) were induced and mapped. Complete maps demonstrated macroreentrant circuits with 1 (n=8) or 2 loops (n=25) rotating around a protected isthmus bounded by two approximately parallel conduction barriers which either consist of a line of double potentials, a scar area of the mitral annulus. A total of 26 critical isthmuses were identified for the 33 VTs mapped, the same isthmus being shared by 2 to 4 different tachycardia morphologies in 5 patients. On average, isthmuses were 31±7 mm long (ranging from 18 to 41 mm), 16±8 mm wide (ranging from 6 to 36 mm) and harbored diastolic electrograms. The isthmus axis was oriented parallel to the mitral annulus plane in perimitral circuits and circuits and perpendicular to the mitral annulus plane in all other circuits. Linear radiofrequency ablation performed across the most accessible part of the isthmus prevented VT recurrence in 19 patients (90%) with a follow-up of 16±8 months.
Conclusions: Detailed 3D electroanatomic mapping is helpful in reconstructing post-infarct VT circuits and in defining the characteristics of their related protected isthmuses. The wide range of isthmus width values supports the need of linear RF lesions to eliminate the reentrant substrate of post-infarct VTs.

P979 Endocardial line ablation during sinus rhythm as first line treatment of post-infarction ventricular tachycardia

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Background: Applicability of radiofrequency ablation (RFA) of post-infarction ventricular tachycardia (VT) has been limited by TV tolerance. Recent studies have described techniques for VT RFA in sinus rhythm. We have developed a strategy including RFA as first line treatment of VT using lack of inducibility of clinical VT as the endpoint.
Objective: To report preliminary results of this treatment strategy in a non-referral VT population with cycle length of 340 ms (range 500-290 ms).
Population: 9 patients (P) aged 56-75 years with an old myocardial infarction (inferior in 7, anterior in 2). Mean left ventricular ejection fraction 32%. In 6 P clinical VT was hemodynamically unstable. VT was recurrent (post ablation) on amiodarone for atrial fibrillation in 2 P, in 7 P it was a first episode. VT was unstable at EP study in 7 P and non-sustained in 2 P.
Methods: VT was induced at baseline. Scar edge was delimited with fluoroscopy-based mapping by change from high to low voltage (<2 mV) electrograms. Clinical VT "exit site" was localised pacing scar edge. Lines were drawn with overlapping, point-by-point RFA applications (8 mm electrode, max 100 W), from the edge to the center of the scar, in different directions, including at least 1 through the exit site.
Results: Ablation included 2-4 lines (total 15-25 points, median 23). Clinical VT became non-inducible in 8 P. A non-clinical VT (cycle <250 ms) was inducible in 3. A defibrillator was implanted in 1 P remaining inducible for clinical VT and 1 with reproducibly inducible non-clinical VT.
Follow-up: The P with inducible clinical VT had multiple VT treated by the defibrillator. The remaining 7 P were free of arrhythmic events after a mean follow-up of 21 month (8-39), including the one with inducible non-clinical VT. Two P died of pump failure: one 20 month after RFA without VT recurrence, the other with an acute myocardial infarction 48 h after RFA.
Conclusion: This preliminary experience suggests that endocardial line RFA of VT substrate in sinus rhythm can be applied to all post-infarction patients with a first episode of VT as first line treatment. Suppression of clinical VT inducibility marks a clinical course free of arrhythmias at mid-term, suggesting no need for defibrillator implantation.

P980 Linear ablation guided by CARTO for control life-threatening ventricular tachycardia in patients with ischaemic cardiomyopathy

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Background: Ventricular tachycardias in patients with low ejection fraction after myocardial infarction can be lifethreatening in spite of ICD implantation because these VT are often incessant or very frequent (electrical storm). In addition, induced VTs are often unstable, preventing extensive mapping to localize all VT circuits.
Methods and Results: Between Mar 2001 and Dec 2002 a total of 12 pts after MI with EF<30%, 2-6 month after ICD implantation were referred for RF ablation because of incessant VT in 1 patient, unmappable polymorphic VT/VF in 1 patient and recurrent VT in 10 patients. Electro-anatomical mapping (EAM)was performed using CARTO system in all but 1 patient (incessant VT) during sinus rhythm. Voltage maps were used to determine the area of dense scar (<0,5 mV), normal myocardium (>1.5 mV) and border zone (>0.5mV and <1.5 mV). Extensive set of linear ablations were done around areas of scar (3 - 6 lines per patient). In patient with incessant VT tachycardia was terminated during 3rd line application. In 3 patients ablation session was repeated because of early VT recurrence after 3-7 days and in 2 patients after 6-7 months. No complications were observed after ablation. Mean fluoroscopy time was 9.2± 4.3 min. No worsening in EF was observed during follow-ups (ECHO). During 3-11 month FU 7 patients are free of arrhythmia (ICD-Holter), In 2 patients after 6-7 months procedure was repeated because of episodes of symptomatic VT terminated by ATP. In further 2 pts 1-2 asymptomatic, ATP terminated VT were recorded. 1 patient died due to heart failure with no arrhythmia in ICD memory.
Conclusion: EAM during sinus rhythm is safe and very useful method to identify target sites for RF lines application especially in patients with severely depressed LV function, unstable and unmappable VT and polimorphic VTs.

ELECTROCARDIOGRAM IN BRUGADA'S SYNDROME, WOLFF–PARKINSON–WHITE'S SYNDROME AND OTHER CLINICAL CONDITIONS

P981 Right precordial early repolarization in Brugada patients and trained athletes: the need for a differential diagnosis

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Background: Brugada syndrome is a cardiac ion channel disease characterized by a distinctive ECG pattern of high take-off ST-segment elevation in V1-V2/V3 ("early repolarization") and the risk of life-threatening ventricular arrhythmias in young people. ECG abnormalities that mimic early repolarization of Brugada syndrome have been reported in up to 8% of young trained athletes.
Methods: In the present study we compared the ECG pattern of right precordial J-point and ST-segment elevation (of 2mm or more) in 30 Brugada patients (aged 34±7years) and 30 healthy trained athletes (aged 22±6 years) in order to identify criteria for differential diagnosis. For the study purpose, the analysis of 12-lead ECG focused on heart rate, conduction times and depolarization/repolarization intervals and abnormalities. The amplitude of maximum ST-segment was measured at J-point (STJ) and after 80 msec (ST80), and a STJ/ST80 ratio was calculated in both subgroups.
Results: Despite similar degree of maximum amplitude of STJ (3.2±1.1mm vs 3.1±0.9mm; p=0.12), Brugada patients had a downsloping ST segment with a STJ/ST80 ratio of 1.7±0.4 as compared with an upsloping ST segment with a STJ/ST80 ratio of 0.73±0.15 in athletes (p<0.0001). A cut off value STJ/ST80 ratio of 1 or more had a sensitivity of 95% and a specificity of 100% for the diagnosis of Brugada syndrome. As compared with athletes, Brugada patients also had a significantly higher heart rate (RR interval of 0.8±0.1 sec vs 1.22±0.21 sec; p<0.0001), a shorter QTc interval (0.35 ±0.04 sec vs 0.39±0.02 sec; p<0.0001) and a longer QRS duration (0.11±0.02 sec vs 0.09±0.01 sec; p<0.0001) as well as exhibited more often a "S1S2S3 pattern" (53% vs 27%; p=0.04). There were no differences between the 2 subgroups with regard to PR interval duration and number of precordial leads (beyond V1) showing inverted T waves.
Conclusions: A STJ/ST80 ratio of 1 or more accurately differentiated the ECG pattern of early repolarization in patients with Brugada syndrome from healthy trained athletes. A longer QRS interval duration and the presence of a "S1S2S3 pattern" refined the diagnosis.

P982 Body surface potential mapping in long-QT syndrome: the role of lead positioning for the identification of patients with ventricular arrhythmias

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Background: The identification of symptomatic patients with long-QT(LQT) syndrome remains difficult in clinical routine. The interpretation of the standard 12-lead ECG has a major impact for the individual risk stratification.
Methods: 14 patients with LQT and ventricular arrhythmias (syncope or survived sudden cardiac death) were enrolled into the study. A 120-channel body surface potential mapping (BSPM) covering the entire torso surface was performed. For all surface leads, the frequency-corrected interval between QRS onset and the maximal T amplitude (QTcmax) was analyzed. The diagnostic value of each lead position of the BSPM was indicated calculating discrimination factors (DF), which for each lead position described the individual difference to the corresponding mean values of a group of healthy subjects (n=11), divided by the standard deviation of this group.
Results: The left-precordial leads of the standard ECG leads presented with high DF levels regarding QTcmax (DF(V5): 2.5±2.0; DF(V6): 2.6±2.0). In the BSPM, inferior lead positions showed even higher values for the discrimination compared to healthy subjects (V7: 3,2±2,6; V8: 3,2±2,9).
Conclusions: Additional ECG recordings in lead V7 and V8 improve the individual identification of patients with long-QT syndrome. In the future, individual risk stratification and the individual strategy for an appropriate therapy may be based on BSPM measurements.

P983 Clinical outcome of asymptomatic individuals with a Brugada-like electrocardiogram pattern

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Background: The ECG pattern of right precordial ST-segment elevation may be associated with life-threatening ventricular arrhythmias and sudden death in young people (so called "Brugada syndrome"). However, this ECG patten is increasingly found in healthy individuals without arrhythmic symptoms. The aim of the present study was to assess the clinical outcome of these asymptomatic individuals with a Brugada-like ECG pattern and to establish prognostic value of programmed electrical stimulation.
Methods: We studied 62 consecutive patients (57 males and 5 females, aged 37±12 years) with the distinctive ECG pattern - spontaneous (56) or induced by sodium channel blockers (6) - characterized by high take-off ST-segment elevation (2 mm or more) in right precordial leads, of either "coved" or "saddleback" type, in the absence of structural heart disease. All patients were asymptomatic and the ECG was obtained during routine examination or at cardiac evaluation because of nonspecific symptoms; a familial form of asymptomatic ECG abnormalities were ascertained in a total of 7 subjects. The occurrence of major arrhythmic events such as cardiac arrest, syncope or appropriate shock discharge by ICD at follow- up was analyzed in all patients. In 26 individuals, who underwent programmed ventricular stimulation (up to 3 extrastimuli from both right ventricular apex and outflow tract), clinical outcome was correlated with the inducibility to sustained polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).
Results: Nine individuals (35%) were inducible to sustained ventricular arrhythmias at PVS (polymorphic VT in 2 and VF in 7), and were treated by ICD (5) or antiarrhythmic drugs (beta-blockers in 2 and amiodarone in one). During a mean follow-up of 35±13 months, none individuals developed symptoms or arrhythmic events.
Conclusions: Asymptomatic individuals with a Brugada-like ECG had a benign outcome during a long term follow-up regardless of results of PVS. These data suggest the need to distinguish between patients with Brugada syndrome (ECG pattern and spontaneous ventricular arrhythmias) and individuals with just a Brugada-like ECG pattern. In this latter subgroup, less aggressive diagnostic and management strategies should be adopted.

P984 The Ajmaline challenge in Brugada syndrome: is it dangerous?

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Background: The Brugada Syndrome (BS) describes a subgroup of patients (pts) without structural heart disease associated with atypical right bundle block and coved-type ST-segment elevation in the right precordial leads at risk for the occurrence of ventricular tachyarrhythmia (VT). The early identification of affected pts is crucial, because at present the implantation of a cardioverter defibrillator is the only safe treatment. The diagnostic ECG pattern can transiently normalize and may be unmasked by sodium channel blockers like ajmaline. Due to anecdotal reports of occurrence of VT during the Ajmaline Challenge we studied the risks of the test.
Methods: During a period of 30 months n=125 pts underwent the Ajmaline Challenge at our institution. Some had either experienced resuscitation from near sudden cardiac death (SCD) (n=16), episodes of unclear syncope (n=71) or VT (n=19). Others had a suspicious ECG at rest (n=31) and/or a family history of SCD or BS (n=24). Target ajmaline dose was 1 mg/kg body weight intravenously under continuous ECG monitoring. Indications to terminate the test were QRS prolongation > 30%, occurrence of the classic Brugada-type ECG or VT.
Results: In n=37 pts (30%) the typical ECG pattern of BS was uncovered. Symptomatic VT appeared in only n=2 pts (2%). Both had a positive reaction to Ajmaline. In one case, the immediate discontinuance of drug supply lead to termination of non sustained VT. The other patient with classic coved-type ECG before the test required multiple defibrillations for sustained polymorphic VT.
Conclusions: (1) The Ajmaline Challenge is a relatively safe method to diagnose BS. It should be performed in the hospital under continuous monitoring. Termination criteria like reaching target dose, QRS prolongation > 30%, presence/appearance of the typical ECG and the occurrence of VT should be met carefully. (2) Due to the prognostic importance of BS all pts with aborted sudden death or syncope of unknown origin without demonstrable heart disease should undergo the Ajmaline Challenge.

P985 Electrocardiographic risk stratification of genotyped patients with long QT-syndrome

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Background: In patients with long QT(LQT)-syndrome, the ECG is used for risk assessment.
Method: To test the value of different ECG-leads regarding risk stratification, discrimination of rate-corrected QT-interval (QTc) of all ECG-leads in 49 genotyped LQT-patients (age: 36 ± 19; LQT1: 25; LQT2: 16; LQT5: 8) between symptomatic (n=21; no of syncope: 7.5 ± 11.2; survived cardiac death: n=10) and asymptomatic (n=28) mutation carriers were studied using Receiver Operating Characteristic Analysis (ROC = area under curve). Additionally, the cut-off values for QTc with the highest sum of sensitivity and specificity for identifying symptomatic patients among LQT mutation carriers were calculated.
Result: In all ECG-leads, QTc was significantly prolonged in symptomatic compared to asymptomatic LQT mutation carriers. The highest discrimination was found in lead II (ROC: 0.85) and lead V6 (ROC 0.82). At a cut-off value of 485 ms in V6, sensitivity was 83% and specificity was 85% for identifying symptomatic mutation carriers. In lead II at a cut-off value of 478 ms 80% and 86%, accordingly.
Conclusion: The surface ECG may help in risk stratification for syncope or sudden cardiac death in patients with LQT syndrome. In our cohort a cut-off value of about 480 ms in lead II or V6 is a reasonable and practicable parameter for identifying LQT patients with a potential risk for symptoms.

P986 Activation-recovery interval measurements in evaluation of global sequence and dispersion of ventricular repolarization in patients

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Background: Activation-recovery interval (ARI) measured from unipolar electrograms has been used as an index of myocardial repolarization time. However, it is unknown if the global sequence and dispersion of ventricular repolarization evaluated using monophasic action potential (MAP) mapping technique could be estimated from the ARI measurements.
Methods: Endocardial MAPs and unipolar electrograms were simultaneously recorded from 34±12 left (LV, n=5) or right ventricular (RV, n=9) sites in 14 patients using the NaviStar catheter and the CARTO system. Local activation time (AT), end-of-repolarization (EOR) time were calculated from the MAPs and the ATs and ARIs from the unipolar electrograms, based on which 14 sets of 3-dimensional maps of global EOR and that of the ARI were reconstructed. The ARI was compared with the EOR at each site. The correlations between the ARI and the EOR, between the ARI and the AT and between the EOR and the AT were analyzed. The global sequence and dispersion of ventricular repolarization were compared for each map.
Results: (1) A significant positive correlation between the ARI and the EOR was found in all the maps, the r value being 0.53±0.27. The mean differences between the ARI and the EOR were 5,57±21 ms for the total 473 paired measurements in the 14 maps (NS). (2) The global dispersion of ARI was 64±15 ms, as compared with that of EOR 68±22 ms (NS). (3) Repolarization sequence was recognizable in 13/14 ARI maps as compared with that in 14/14 EOR maps. (4) ARI sequence was similar to the EOR sequence in 12/14 maps. (5) The ARI was positively correlated with the AT in 12/14 maps, as compared with that between the EOR and the AT in 14/14 maps.
Conclusion: The ARI measurements from the unipolar electrograms well-estimated the EOR measurements from the MAPs, suggesting the usefulness of the former method in evaluation of ventricular repolarization.

P987 Is it possible to distinguish Brugada syndrome patients with a SCN5A mutation from those without using phenotypical characteristics?

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Introduction The Brugada syndrome (BS) is an inherited cardiac disease characterized by a varying degree of ST-segment elevation in the right precordial leads, and (non) specific conduction disorders. BS patients may develop malignant ventricular arrhythmias.
In a minority of patients mutations in the gene encoding the cardiac sodium channel (SCN5A) can be found. Genetic heterogeneity has been demonstrated but other casually-related genes await identification.
We have tested whether a genotype-phenotype relation exists in BS by trying to distinguish BS patients with (carriers) and without (non-carriers) a SCN5A mutation using clinical parameters. Existence of such a relation might facilitate genetic screening.
Methods In a multi-center study we have collected data on; demographics, clinical and family history, ECG parameters, HV interval and ECG parameters after pharmacological challenge with INa blocking drugs, in BS patients with (n=23) or without (n=54) an identified SCN5A mutation (genetic screening by SSCP).
Results The two groups did not differ in demographics, clinical or family history. Carriers had a significantly longer PQ interval on the baseline ECG (209±51ms vs 163±25ms ($p<0.001$)) and a significantly longer HV-time (66±13 vs 48±9ms ($p<0.001$)). A PQ interval of >=210ms predicts the presence of a SCN5A mutation with a sensitivity of 48% a specificity of 98% a positive predictive value of 92% and a negative predictive value of 81% ($p<0.0001$). For a HV interval >=60ms values were respectively 88%, 82%, 50% and 97% ($p<0.001$). After infusion of INa blocking drugs carriers had a significantly longer PQ interval (222±37ms vs 195±33ms ($p<0.05$)) and QRS interval (142±31ms vs 118±21ms ($p<0.005$)). Carriers also had more increase in QRS duration (38±31ms vs 18±18ms ($p<0.05$)).
Conclusion We observed significant longer conduction intervals (PQ, HV and QRS increase upon class I drugs) in patients with established SCN5A mutations. These results concur with the observed loss of function (i.e. reduced sodium current) of mutated BS-related sodium channels. BS patients with and without a SCN5a mutation can be differentiated with a high specificity on the basis of phenotypical differences.

P988 Usefulness of the 12-lead electrocardiogram for locating the site of origin of idiopathic left and right ventricular outflow tract tachycardia

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Background and Purpose: Pace mapping is the most efficient technique for locating the successful ablation site of an idiopathic ventricular tachycardia (IVT) originating from the right or left ventricular outflow tract (RVOT, LVOT). This study was aimed at analysing the 12-lead QRS characteristics during pacing from different sites of the RVOT and LVOT to obtain useful criteria for predicting site of origin of these VT.
Methods: We prospectively studied 24 patients without structural heart disease undergoing catheter ablation of a left accessory pathway by a transaortic approach. To mimic spontaneous tachycardia, continuous pacing at twice the diastolic threshold and a 350 ms coupling interval was performed from the distal electrode pair of a 4 mm tip ablation catheter at 10 different sites on the LVOT, aortic cusps and RVOT. A 12-lead ECG was recorded during pacing at each site where ventricular capture was successful. ECG's were analysed for QRS pattern, axis and width, the point of precordial transition, QRS morphology in leads I, aVL, aVR, V5 and V6, r wave amplitude in V1, and delta wave-like beginning of the QRS.
Results: V2 transition was not observed when pacing from the RVOT but in 26% of patients when pacing from the LVOT or aortic cusps. V3 transition was observed in 9% of cases paced from the RVOT, in 32% from the LVOT and 56% from the aortic cusps. In 20% and 26% respectively, of LVOT and aortic cusp pacing occasions, transition was obtained in V4. The presence of a s wave in V5 or V6 predicted a LVOT pacing site (51,5% sensitivity, 95% specificity, 66% + predictive value and 88% - predictive value). An rS, RS or Rs morphology in lead I was the best predictor for left aortic cusp or mitroaortic continuity pacing (87,5% sensitivity, 90% specificity, 89,7% + predictive value and 88% - predictive value). QRS was significantly narrower in septal LVOT (143 ± 22 ms vs. 170 ± 12; $p < 0.001$) than in the other pacing sites.
Conclusions: Precordial transition, and the presence of s wave in leads I, V5 and V6 were the most useful criteria for determining the pacing site from the LVOT and RVOT. Although a left bundle branch block morphology, inferior axis, late transition is the only pattern obtained during pacing from the RVOT, different sites from the LVOT and aortic cusps can origin this morphology.

P989 Distinct electrocardiographic patterns for right ventricular outflow tract tachycardia – Verification of electrocardiogram algorithms by CARTO

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Right ventricular outflow tract tachycardia (RVOT-T) originates from RV free wall (A-anterior) vs septal (P-posterior) side, left (L) vs right (R) side and proximal (S-superior) vs distal (I-inferior) side below pulmonic valve. Identification of these sites of origin (SOO) using ECG criteria facilitates localization during catheter ablation (CA). Prior attempts to identify ECG patterns by pace mapping at these sites using body surface ECG mapping (BMS) and fluoroscopy (F) alone were limited by reproducibility of localization. Methods and Results: To overcome this limitation we used CARTO (electro-anatomic mapping - EAM) for precise localization of RVOT-T SOO based on activation and propagation maps obtained in 23 pts who underwent successful CA for RVOT-T and analyzed 12 lead ECG during RVOT-T or VEB identical with RVOT-T. The ECGs were analyzed for QRS amplitude/width, morphology and patterns of precordial transition (table below).

ECG Patterns

A vs P	QRS>140ms	QRS<140ms	II,III:RR', Rr'	II,III: R
A (6)	5	1	1	5
P (17)	16	1	7	9
L vs R	aVR <aVL	aVR>aVL	I negative	I: positive
L (17)	8	9	9	8
R (6)	3	3	3	3
S vs I	V1, V2 initial r>0.2mV	V1, V2 initial r<0.2mV		
S (18)	10	8		
I (5)	2	3		

It was found, that posterior RVOT-T SOO obtained by EAM was accompanied with a sharp R wave without any notching in lead II and III QRS complex ($p<0.05$). Similarly, inferior RVOT-T SOO localization coexisted with low r amplitude (< 0.2 mV) in V1 and/or V2 QRS complexes. Conclusion: EAM would potentially allow developing ECG algorithms to facilitate rapid arrhythmia localization during CA for RVOT-T.

P990 The individually derived formulae are superior to Bazett and Fridericia formulae for heart rate correction of the QT interval

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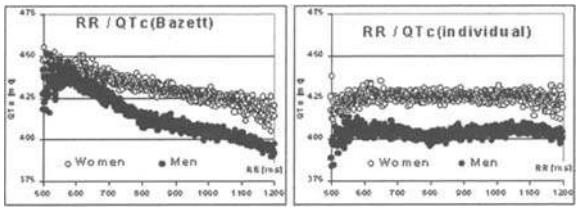
Background: It is considered that most formulae for heart rate correction of the QT interval over- or undercorrect the QT interval at extreme heart rates, but perform satisfactorily at physiological resting heart rates. We compared Bazett and Fridericia formulae with an individually derived heart rate correction formula over a wide range of physiological heart rates.
Methods: 24-hour 12-lead digital ECGs (SEER MC, GE Marquette, one 10-second ECG every 30 sec, 2880 ECGs/24 hours) were recorded in 22 healthy men (age 27±7 years) and 24 healthy women (27±8 years). The QT intervals of all ECGs were measured automatically (QT Guard, GE Marquette, downslope inflex tangent method). In each subject, all QT intervals were corrected by 1) Bazett formula, 2) Fridericia formula and 3) by an individual formula QTc=QT/RR(power of beta), where the optimum value of beta was derived in each subject by a power model QT = alpha + (RR)(power of beta), which was best-fitted to her/his 24-hour QT/RR data. The linear correlations between the RR intervals and QTc(Bazett), QTc(Fridericia) and QTc(individual) were estimated.
Results: Even within the physiological range of resting heart rate (i.e. 60-90 beats/min), QTc (Bazett) and QTc(Fridericia), were significantly correlated to the RR interval (Bazett: r=-0.87 and r=-0.92 in women and men, respectively; Fridericia: r=0.90 and 0.54). QTc(individual) was not correlated to the RR interval (r=-0.06 and 0.09 in women and men, respectively).



Conclusion: Both Bazett and Fridericia formulae may over- or undercorrect the QT interval even at physiological heart rates. Correction formulae derived in each subject from her/his 24-hour QT/RR data provide superior heart rate correction of the QT interval.

P991 Prevalence of a wide QRS complex in candidates to coronary artery bypass grafting and relationship with clinical outcome

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We investigated the prognostic weight of several factors on the risk of heart failure in patients undergoing CABG. We followed 300 consecutive patients up to 1 year after surgery to assess clinical outcome, presence and degree of heart failure. The risk of developing heart failure > class 2 at 1 year was investigated by logistic regression on the following preoperative variables: sex, age, left ventricular EF, NYHA class, QRS duration, previous MI, previous CABG, previous class 3 or 4 heart failure (PHF), atrial fibrillation (AF), history of ventricular arrhythmias, hypertension, hypercholesterolemia, diabetes, coexistent non-cardiac disease. Age was 70±8 years and EF was 52±13% at the time of surgery. Average follow up was 19±8 months. Heart failure > class 2 occurred in 108/300 patients (36%) at 1 year. Among the abovementioned clinical variables, only sex,previous severe heart failure, coexistence of AF, and QRS duration were predictive of heart failure development at follow up (table). All the other variables were not risk markers for heart failure at logistic regression. Heart failure > class 2 developed in 67/84 patients with QRS>130 ms vs 41/216 with QRS<130 ms ($p < 0.01$).

		OR	95% CI
Female sex	66/300	5.9	2.3- 15.4
PHF	101/300	3.2	1.4-7.1
Atrial Fibrillation	19/300	11.4	1.3-100
QRS duration (ms)	108±19	1.22	1.16-1.30

CI=confidence interval; OR=odds ratio; PHF=previous class 3 or 4 heart failure.

Forty-six patients (15%) had QRS>140 ms suitable for LV-based pacing. In the current surgical era, candidates to CABG (50% older than 70 years) have a relevant likelihood of heart failure at follow up, despite myocardial revascularisation. Risk stratification may rely upon inexpensive variables as previous severe heart failure, presence of AF, and QRS duration. A minority of patients could benefit from LV-based pacing, which should be considered at the same surgical time of CABG via an epicardial implantation.

P992 The role of resting electrocardiogram in the assessment of viable myocardium in ischaemic cardiomyopathy; comparison with positron emission tomography

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Objectives: We assessed the value of ST-segment elevation at rest to identify viability in the anterior wall in pts with anterior wall akinesia and depressed LV function; the results were related to positron emission tomography (PET) and coronary angiography.Methods:32 pts (29 male, age 63±8 years, LVEF 31±8) with chronic ischemic cardiomyopathy had a 12-lead ECG recorded at rest, and underwent PET with fluorine-18-fluorodeoxyglucose(FDG), and coronary angiography. The extent of ST-segment elevation (mm) was calculated from leads V1-V6, I and aVL. Uptake of FDG in the anterior wall >50% of the maximum uptake indicated the presence of viable myocardium. Coronary stenoses >70% were considered critical.Results: Based on the PET results, 21 pts were classified as viable and 11 as nonviable; 11/21 (52%) PET-viable pts showed ST-segment elevation <1 mm in 1 or more anterior leads, as compared to only 1/11 (9%) pts with scar tissue (OR 11, CI 95% 1.1-101.9, p= 0.02). Mean ST-segment elevation at rest was significantly lower in the viable as compared to the nonviable pts in leads V2 (1.07±0.61 mm vs 1.76±0.49 mm, p=0.003), V3 (0.81±0.61 mm vs 1.79±0.55 mm, p= 0.0001), V4 (0.24±0.48 mm vs 1.35±1.12 mm, p=0.0005) and V5 (0.03±0.15 mm vs 0.57±0.87 mm, p=0.009). ROC curve analysis identified ST-segment elevation <1 mm in lead V3 as the optimal cut-off for identifying viable myocardium (sensitivity 76%, specificity 91%, AUC 0.87). At coronary angiography, 13 pts with viability at PET had an occluded left anterior descending coronary artery (LAD) with collateral circulation and 8 had a critical stenosis. Among the 11 pts without viable tissue 6 had an occluded LAD (in 4 cases with collateral vessels) and 5 had a critical stenosis.
Conclusions: ST-segment elevation<1 mm in lead V3 is an accurate marker to identify the presence of viable tissue, in pts with ischemic cardiomyopathy and akinesia of the anterior wall. This electrocardiographic pattern is frequently correlated with multivessel disease and presence of coronary collaterals to the occluded vessel.

P993 Natural history of Brugada syndrome: insights for a novel risk stratification algorithm

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Brugada syndrome (BS) is an inherited arrhythmogenic disease characterized by increased risk of sudden cardiac death in young individuals. BS is characterized by a wide spectrum of manifestations ranging from completely asymptomatic individuals to highly malignant variants with recurrent life-threatening events. However, the clinical approach to BS patients is made difficult by the incomplete information on the natural history of the disease and by the conflicting evidences on the predictive role of programmed electrical stimulation (PES). In this study we present data on a large group of BS patients and propose a new risk stratification scheme. Clinical data were collected for 200 consecutive patients (152 men; age 41±18 years) diagnosed as BS by the presence of the typical ECG abnormalities (ST elevation in V1-V3 ad right bundle branch block) either spontaneously or after administration of sodium channel blocker (Flecainide 2mg/kg or Ajmaline 1mg/Kg, i.v.). Genetic analysis was performed and mutations on the SCN5A gene were identified in 28/130 (22%) probands. The analysis of cardiac events between birth and the last follow up documented cardiac arrest (CA) in 22 individuals (20 males; 33±13 years); 5/22 (23%) patients experienced multiple CAs. History of syncope was present in 34/200 patients (17%). A family history of unexplained sudden death was present in 26/130 (20%) probands. Multivariate analysis showed that patients at higher risk for CA are those with a combined presence of spontaneous ST segment elevation in V1-V3 and history of syncope (HR 6.4; 95% CI 1.9-21; p<0.002), while patients with a spontaneous ST segment elevation without syncope constitute a group with moderately increased risk (HR 2.1; CI 0.68-6.9). On the other hand, PES showed fairly good sensitivity (66%) but a very low specificity (34%) in predicting CA and no statistically significant association between inducibility and occurrence of ventricular fibrillation was identified.
In conclusion, this study provides for the first time data on the natural history of BS in a large cohort of patients and in the largest reported group of genotyped individuals. Risk stratification of BS patients based on the clinical presentation allows the identification of those individuals at higher risk. Our data also show that inducibility at PES has a very low specificity and point to the need of specifically assessing its predictive value with specific protocols.

DIABETES AND ATHEROSCLEROSIS

P994 Insulin enhances vascular cell adhesion molecule-1 (VCAM-1) expression in human endothelial cells

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Hyperinsulinemia has been proposed among the causes of accelerated atherosclerosis in non-insulin-dependent diabetes mellitus (NIDDM). The expression of several endothelial leukocyte adhesion molecules has a critical role in the initiation and progression of atherosclerosis. We hypothesized that insulin, alone or in the presence of submaximal concentration of lipopolysaccharide (LPS), a well-known inducer of endothelial activation, may directly affect the expression of endothelial leukocyte adhesion molecules in the endothelium and, particularly, the expression of vascular cell adhesion molecule (VCAM)-1, intimately involved in early atherogenesis. Human umbilical vein endothelial cells (HUVEC), at passage 4-5, were incubated with insulin for 24 hours, at concentrations ranging from 0.01 to 100 nmol/l, thus covering a range from low physiological to high pharmacological levels, followed by co-incubation with LPS for further 0-24 hours. After this time, VCAM-1, E-selectin and ICAM-1 expression were assessed by cell surface immunoassay (EIA). At none of the concentrations tested, insulin showed any cytotoxicity. VCAM-1 levels (mean ± SD, with 5 replicates in each condition) at the various insulin concentrations, expressed as percent of control, were as in Table.

Effects of insulin on VCAM-1 expression

	Insulin				
	0.01 nmol/L	0.1 nmol/L	1 nmol/L	10 nmol/L	100 nmol/L
no stimulus	97 ± 20	94 ± 27	134 ± 57*	145 ± 61*	158± 76*
with LPS 0.1 ng/mL	99 ± 8.3	105 ± 11	170 ± 64	243 ± 87*	229 ± 70*

values are expressed as mean ± SD, as % of control. *=P<0.05

Thus, at concentrations of 10 and 100 nmol/l, pretreatment with insulin significantly potentiates the induction of VCAM-1, but not of ICAM-1 and E-selectin, by LPS. Moreover, at concentrations ranging from 1-100 nmol/l, insulin alone (in the absence of LPS) is sufficient to induce VCAM-1 induction. This might increase vascular inflammation in vivo and thereby foster atherosclerosis in hyperinsulinemic subjects with NIDDM.

P995 Vitamin C improves endothelial function in type II diabetic patients with coronary artery disease but not in patients with diabetes only

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Background: Oxidative stress is an important mechanism of endothelial dysfunction observed in patients with coronary artery disease (CAD) or diabetes mellitus (DM). However, the possible role of antioxidant administration in diabetic patients, is still unclear. In this study we examined the effect of chronic treatment with vitamin C on endothelial function in diabetic patients of type 2 with or without CAD.
Methods: In a double-blind placebo-controlled study, 38 patients (30 males, 8 females, aged 65±1.6 years) with DM of type 2, were enrolled. 26 of them had angiographically established CAD while the rest of them had no clinical evidence for the disease. 11 patients with CAD+DM (group A) and 7 patients with DM only (group B) received vitamin C 2g/d for 4 weeks. 15 patients with CAD+DM (group C) and 5 patients with DM only (group D) received placebo for the same period of time. Forearm blood flow was measured using venous occlusion strain-gauge plethysmography, at baseline and after treatment. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to post reactive hyperemia blood flow. Endothelium independent flow (NTG%) was expressed as the % change from baseline to post sublingual nitroglycerin administration flow.
Results: Basal blood pressure, heart rate, body weight, basal forearm blood flow and NTG% remained unchanged in all groups. All values are expressed as mean±SEM. FMD and NTG% were not significantly different between patients with CAD+DM (51.5±6.0 and 61.0±6.4% respectively) or DM (53.3±9.1 and 71.7±12.8% respectively, p=NS). FMD in groups A, B, C and D was before treatment: 66.5±11.6%, 53.8±11.2%, 36.3±6.3% and 55.2±12.1% respectively and after treatment: 84.3±15.1% (p<0.05), 55.6±6.9%(p=NS), 36.3±3.4%(p=NS) and 56.8±7.9%(p=NS) respectively.
Conclusions: Chronic administration of vitamin C seems to improve endothelial function only in patients with combined coronary artery disease and diabetes mellitus of type 2, while it is not effective in diabetic patients without coronary artery disease.

P996 Vitamin C and Insulin therapy decrease factor VIIa and insulin improves fibrinolytic activity in type 2 diabetes (T2DM)

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Background: Post-prandial lipaemia (PPL) is associated with an elevation of factor VIIa, a potent procoagulant, initiating the thrombotic response to atheromatous plaque rupture. Factor VIIa increases after a fatty meal, correlates with the degree of postprandial (PP) triglyceridaemia and seems related to free fatty acid production during lipolysis of TG-rich lipoproteins by lipoprotein lipase on the endothelial cell surface. There is also evidence that PAI-1 activity/antigen is increased acutely after a fat load. This infers relative fibrinolytic resistance 2 and 4 hours after a fatty meal. Vitamin C blunts PPL induced endothelial dysfunction/damage and may attenuate PP elevations in FVIIa. Insulin therapy increases LPL activity attenuates TG rises post-prandially. Insulin therapy in NIDDM may decrease PAI-1 activity by decreasing VLDL levels by upregulating LPL activity.
Methods: 18 T2DM subjects with moderate glycaemic control and no overt vascular disease were studied. All subjects had an overnight fast and received a standard fat meal. Lipid profiles, activated factor VII (ng/ml), PAI-1 (UA/ml) were measured in the fasting and PP phase over 8 hours. The study was repeated in a double-blinded manner with placebo/oral VC (1g) prior to meal then randomized to either VC/placebo and Insulin therapy for 3 months. A repeat fatty meal was then ingested and the experiment repeated.
Results (Mean±SD) There was a significant decrease in factor VIIa at 0, 4 and 8 hrs in response to PPL with VC; 7.6±1.3 to 4.97±1.2 (0hrs), 6.7±1.2 to 4.8±1 (4hrs) and 6.24±0.7 to 5.3±0.5 at 8hrs. Insulin also decreased factor VIIa to 4.25±1, 4.45±1.4 and 4.45±1.4 respectively (p<0.05). In response to insulin therapy there was a significant decrease in PAI-1 levels at 4 and 8hrs PP, 29.1±3.1 to 25,1±3.3 (0hrs), 20.5±3 to 13.8±2.2 (4hrs) and 23.3±1.6 to 18.37±1.3 (8hrs), p<0.05. There was no change in tPA levels.
Conclusion: Vitamin C and Insulin therapy attenuates factor VIIa levels postprandially in T2DM after a fatty meal. Insulin therapy also decreases PAI-1 levels at 4 and 8 hours postprandially. Therefore both Vitamin C and insulin therapy in T2DM, have beneficial effects on the thrombogenic mileu postprandially. In particular insulin has additional effects on the fibrinolytic system by decreasing PAI-1, possibly by decreasing VLDL levels and improving endothelial function.

P997 Effects of diabetes on endothelial function and adhesion molecules serum levels, in patients with or without coronary artery disease

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Background: Diabetes mellitus (DM) and coronary artery disease (CAD) are both associated with endothelial dysfunction. Serum levels of soluble vascular cell adhesion molecule (sVCAM-1) and soluble intercellular adhesion molecule (sICAM-1) are increased in patients with CAD. However, the effect of combined CAD and diabetes mellitus on endothelial function and on serum levels of sICAM-1 and sVCAM-1 is not well studied.
Methods: We studied 19 patients with CAD without DM (Group A), 11 patients with CAD+DM (group B), 11 patients with DM without CAD (group C) and 11 healthy controls without CAD or DM (group D). Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to post reactive hyperemia blood flow. Endothelium independent flow (NTG%) was expressed as the % change from baseline to post sublingual nitroglycerin administration flow. Serum levels of sVCAM-1 and sICAM-1 were determined using an immunosorbent assay (ELISA) and expressed in ng/ml. All values were expressed as mean±SEM.
Results: FMD was not significantly different between group A (68±7%) and C (72±19%). FMD was significantly less in group B (51±3.7%) compared to groups A (p<0.05), C (p<0.05) and D (111±17%, p<0.01). FMD was significantly greater in group D compared to groups A and C (p<0.05 for both). NTG% was not significantly different between the groups. Serum levels of sICAM did not differ between groups (280±35, 297±45, 250±19 and 243±22 ng/ml in groups A, B, C and D respectively). Serum levels of sVCAM-1 were significantly greater in groups B (484±43 ng/ml) and C (585±67 ng/ml) compared to groups A(358±25 ng/ml, p<0.05 for both) and D (340±21 ng/ml, p<0.05 for both).
Conclusions: Both diabetes mellitus and coronary artery disease are associated with endothelial dysfunction. sVCAM-1 serum levels are elevated in patients with diabetes mellitus with or without coronary artery disease. These findings indicate that the inflammatory process with the contribution of endothelial dysfunction, might be a connective link between diabetes of type II and coronary atherosclerosis.

P998 Comparison of dobutamine stress echocardiography and dobutamine stress scinitigraphy to asses the prognosis of patients with diabetes mellitus

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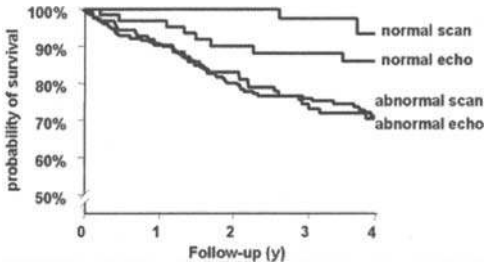
Purpose: This study compares the incremental prognostic value of dobutamine stress echocardiography and dobutamine stress myocardial perfusion imaging in patients with diabetes mellitus.
Background: Dobutamine stress testing is a safe and feasible technique for the assessment of prognosis, especially in patients unable to perform an exercise test. However, the relative prognostic value of DSE and DSMPI in patients with diabetes mellitus has not been evaluated.
Methods: A total of 603 diabetic patients unable to perform an exercise test underwent DSE (396 patients) or DSMPI (207). Follow-up was successful in 597 of 603 (99%) patients. End-points during follow-up were hard cardiac events (cardiac death and nonfatal myocardial infarction) and all causes of mortality. An abnormal DSE was defined as the presence of wall motion abnormalities at rest or an ischemic response. An abnormal DSMPI was defined as the presence of fixed and/or reversible perfusion abnormalities.
Results: DSE was considered abnormal in 324 patients (82%). An abnormal DSMPI was present in 125 (64%) patients. A multivariable Cox proportional-hazard model demonstrated that both the presence of an abnormal DSE and an abnormal DSMPI provided incremental prognostic information to clinical data. Figure 1 compares hard cardiac event rates. Normal DSMPI vs abnormal DSMPI: $p<0.0005$. Normal vs abnormal DSE: $p<0.05$. Normal DSMPI vs normal DSE p=0.6. Abnormal DSMPI vs abnormal DSE p=0.4.



DSE versus DSMPI.

Conclusions: DSE and DSMPI are safe and useful methods for the prognostic stratification in patients with diabetes mellitus unable to perform an exercise test. Patients with normal DSE or DSMPI have a good prognosis, whereas patients with an abnormal test are at a high risk of cardiac events.

P999 Tumor necrosis factor-alpha impairs insulin-stimulated endothelium-dependent vasodilatation and glucose uptake in humans

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Aim: Tumor necrosis factor-alpha (TNF) is elevated in patients with type 2 diabetes and inhibits insulin-stimulated glucose uptake in animal models and in vitro. It may thus be a mediator of insulin resistance. The aim of this study was to examine whether TNF acutely inhibits insulin-stimulated endothelium-dependent vasodilatation and glucose uptake in humans. **Methods:** Lean healthy men were studied in the fasting state. Drugs were infused into the brachial artery measuring blood flow by venous occlusion plethysmography, expressed below in units of ml/[100 ml tissue]/min. Acetylcholine was used as endothelium-dependent agonist and nitroprusside as endothelium-independent agonist. Each study was based on three infusion series given the same day: infusing first the agonist alone, then co-infusing insulin and the agonist and finally co-infusing TNF, insulin and the agonist. TNF and insulin were infused at a constant rate of 17 ng/min and 0.05 mU/Kg/min. For control, TNF and insulin were replaced by their vehicle in separate groups of volunteers. Glucose uptake was measured as the product between the arterial-venous difference of plasma glucose and forearm blood flow and expressed in mM/Kg/min.
Results: During insulin infusion plasma insulin rose from 3.7±0.3 to 98.8±8.3 mU/L in venous effluent blood from the perfused arm and to 5.6±0.4 mU/L in samples from systemic blood. During TNF infusion, local and systemic plasma TNF rose from 1.4±0.5 to 134±36 and 6.5±1.4 ng/L respectively. The flow under maximal acetylcholine stimulation was 12.7±2.3. Insulin enhanced this flow by 22% (p=0.0007). When TNF was co-infused with insulin forearm flow decreased by 32% to 8.6±2.3 (p=0.002). Neither insulin nor TNF had an effect on the nitroprusside response (p=0.7). Insulin infusion increased glucose uptake by 1.0±0.1 (p=0.02) but in the presence of TNF, insulin had no effect on glucose uptake, which changed by -0.2±0.3 (p=0.5)
Conclusion: TNF blunts both insulin-stimulated endothelium-dependent vasodilatation and insulin-stimulated glucose uptake in the human forearm. This findings support the hypothesis of the involvement of TNF in diabetes-related atherosclerosis.

P1000 Effects of vitamin C on endothelial function in diabetic patients with coronary artery disease: a double blind placebo controlled study

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Background: Oxidative stress plays a key role in the pathogenesis of endothelial dysfunction in coronary artery disease (CAD) and diabetes mellitus (DM). In this study we investigated whether treatment with the antioxidant vitamin C improves endothelial function in patients with CAD and DM of type I or II.
Methods: In a double-blind placebo-controlled study, 49 patients (42 males, 7 females, aged 64±1.2 years) with CAD and DM, were enrolled. 23 of them were of type I DM and 26 of type II. 19 diabetic patients (8 with type I DM (group A) and 11 with type II DM (group B)) were treated with vitamin C 2g/day for 4 weeks. The remaining (15 with type I DM (group C) and 15 with type II DM (group D)) received placebo for 4 weeks. Forearm blood flow was measured using venous occlusion strain-gauge plethysmography, at baseline and after treatment. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to post reactive hyperemia blood flow. Endothelium independent flow (NTG%) was expressed as the % change from baseline to post sublingual nitroglycerin administration flow.
Results: Basal blood pressure, heart rate, body weight, basal forearm blood flow and NTG% remained unchanged in all groups. All values are expressed as mean±SEM. FMD was similar between patients with type 1 (51.7±5.1%) and type 2 (54.7±8.1%, p=NS) DM. After treatment, FMD was significantly increased in groups A (from 56.5±6.5 to 81.4±9.2% $p<0.05$) and B (from 66.5±11.7 to 84.3±15.1% $p<0.05$) while remained unchanged in groups C (from 53.1±4.2 to 50.1±8.2% p=NS) and D (from 55.8±11.6 to 58.3±10.1% p=NS).
Conclusions: Chronic administration of vitamin C seems to improve endothelial function in patients with combined coronary artery disease and diabetes mellitus of type I or II. This finding indicates a possible beneficial role of vitamin C in these patients.

P1001 Does ramipril have influence on antioxidant profile in type 2 diabetics?

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Oxidative stress and free radical injury are important in initiation and progression of accelerated atherogenesis in diabetics. We previously shown that antioxidant profile in diabetics are strongly influenced by the quality of metabolic control and plasma lipid levels. Recent studies suggested that ramipril can delay the progression of atherosclerosis, cardiovascular morbidity and mortality in high-risk population independently of its antihypertensive effect.
The study was aimed to estimate antioxidant effects of ACE-inhibition (ACEI) in obese, Type 2, normotensive diabetics with no angiographically and no clinically manifest coronary artery disease. Baseline characteristics of the study group were: n= 20, sex ratio female/male=11/9, mean age 47.5±3.5 years and duration of diabetes 3.5±1.2 years. All patients were on antidiabetic diet and gliclaside therapy and metabolic control was satisfied in all (HbA1c<7.5%). Antioxidant profile was estimated by: Erythrocyte Superoxide Dismutase (E-SOD; U/gHb), Erythrocyte Glutathione Peroxidase (E-GPx; U/gHb) activity and Plasma Total Antioxidant Status (P-TAS; mmol/l). All parameters were determined by spectrophothometric methods. Plasma triglyceride (TG; mmol/l), total cholesterol (Tot-Ch; mmol/l) and HDL cholesterol (HDL-Ch; mmol/l) were measured by enzymatic methods. LDL cholesterol (LDL-Ch; mmol/l) and LDL/HDL ratio were calculated. Blood samples were taken before and one month after ACEI (ramipril, 5 mg bid).
Results: after ramipril therapy the metabolic control remain unchanged (HbA1c: 7.2±0.5 vs. 7.0±0.3), as well as TG (1.8±0.6 vs. 1.7±0.5, p> 0.05), Tot-Ch (6.5±0.4 vs. 6.0±0.6 p> 0.05), LDL-Ch (4.2±0.4 vs. 3.9±0.5, p>0.05) and HDL-Ch (male: 1.32±0.05 vs. 1.29±0.05, p>0.05; female: 1.55±0.03 vs. 1.45±0.03, p>0.05). In comparison with the initial values E-SOD activity was markedly increased by 41% (635±55.5 vs. 895±43.5, $p<0.05$), E-GPX was increased by 2.25% (26.7±6.75 vs. 27.3±5.23, p>0.05) and increment of P-TAS was 13.93% (1.22±0.25 vs.1.39±0.20, p>0.05).
Conclusion: In type 2 diabetics one month of ramipril therapy improved antioxidant status independently of the quality of metabolic control and plasma lipid levels. It can be consider that this effect might be associated with angiotensin II suppression and its influence on oxygen free radicals production.

P1002 Atorvastatin and micronized fenofibrate, alone and in combination, in type-2 diabetes mellitus with combined hyperlipidemia

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Objective: The study evaluated the effect of the atorvastatin-fenofibrate combination on lipid profile, in comparison to each drug alone, in patients with type-2 diabetes mellitus (DM) and combined hyperlipidemia (CHL).
Research design and methods: One hundred and twenty consecutive patients, free of coronary artery disease (CAD) at entry, were studied for a period of 24 weeks. These were randomly assigned to atorvastatin (20 mg/day,n=40), micronized fenofibrate (200 mg/day,n=40) or combination of both (atorvastatin 20 mg/day plus fenofibrate 200 mg/day,n=40). The effect of treatment on low density lipoprotein cholesterol (LDL-C), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), apolipoproteins A-I and B, lipoprotein (a), and plasma fibrinogen (PF) was recorded. Moreover, the percentage of patients that reached the American Diabetes Association (ADA) treatment goals and the estimated CAD risk status were calculated.
Results: No patient was withdrawn from the study because of side-effects. The atorvastatin-fenofibrate combination reduced total cholesterol by 37%, LDL-C by 46%, TG by 50% and PF by 20%, while it increased HDL-C by 22% ($p<0.0001$ for all). These changes were significantly better than those of both monotherapies. From patients on drug combination 97.5% reached the LDL-C treatment goal of <100 mg/dl, 100% the desirable TG levels of <200 mg/dl, and 60% the optimal HDL-C levels of >45 mg/dl. These rates were significantly higher than those of both monotherapies. Combined treatment reduced the 10-year probability for myocardial infarction from 21.6% to 4.2%.
Conclusions: The atorvastatin-fenofibrate combination has a highly beneficial effect on all lipid parameters and plasma fibrinogen in patients with type-2 DM and CHL. It improved patients' CAD risk status significantly more than each drug alone.

P1003 Perfusion abnormalities detected by SPECT imaging are closely related to carotid intima-media-thickness in asymptomatic diabetic patients

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Background: Myocardial perfusion defect documented by stress SPECT imaging has been reported to be a long term prognosis marker in totally asymptomatic type 2 diabetic patients (TAD). The carotid intima-media thickness (CIMT) has been proposed recently as a new marker predictive of major cardiovascular events in high risk patients but no data exist in TAD patients. We evaluated the relation between CIMT and SPECT in a TAD population. Methods. From 01/00 to 12/00, CIMT was automatically measured by high resolution ultrasonography using a specific software in 52 TAD patients pts (mean age 60 years, range 49-75) without history of heart disease who underwent a rest Thallium 210/stress Tc-99m sestamibi SPECT imaging screening because of a diabetes duration > 10 years plus at least one additional risk factor. Results: 20 pts had had SPECT+, 32 SPECT-. They did not differ for age (62±8 vs 60±8, p=0.45) and duration of diabetes (14±6 versus (vs) 13±6; p=0.63); number of risk factor (2.6±8 vs 1.9±8; p=0.0046), male proportion (65% vs 34%; p=0.046) and CIMT (0.64±0.1 vs 0.55±0.09; p=0.0052)were higher in SPECT+ than SPECT-. Multivariate analysis using multiple logistic regression model showed that CIMT was the variable that best correlated with positive SPECT imaging: odd ratio 2.8, CI: [1.32;5.92], p=0.0074.
Conclusions: CIMT appears to be strongly correlated with positive SPECT imaging in high-risk diabetic asymptomatic patients and might represent an alternative screening test in this population.

P1004 The elusive link between insulin-resistance and ultrasonic indices of early cardiovascular damage in essential hypertensives

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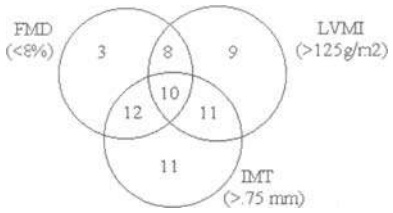
Background: Insulin resistance has been proposed as the metabolic basis of atherogenesis. The association between hypertension, insulin resistance and early signs of cardiovascular damage is incompletely understood.
Aim: to determine the relationship between insulin-resistance and ultrasonically assessed early target organ damage in essential hypertensives.
Methods: 71 asymptomatic non diabetic essential hypertensives (36 females, age= 57 ± 11 years, weight: 81±15 kg) with negative maximal cardiac stress testing underwent, on different days and in random order: 1) Insulin-resistance calculation using the Homeostasis Model Assessment (HOMA); 2) an ultrasound study of carotid (intima-media thickness,IMT), cardiac (left ventricular mass index, LVMI), and brachial (% flow mediated dilation, FMD) district.
Results: IMT was 0.9.±0.30 mm; % FMD was 8.5±6.7; LVMI was 131±36 g/m^2. The mean HOMA was 2.29±1.19. HOMA was not significantly related to LVMI (r= -0.025, p= 0.8), FMD (r=-0.145,p=0.2) and IMT (r= - 0.09,p=0.4). %FMD was weakly correlated to LVMI (r=- 0.24,p=0.04) and carotid IMT (r=-.33,p=0.004),whereas no correlation existed between IMT and LVMI (r= 0.14, p=0.23). At individual patient analysis, an abnormality of at least 1 in % FMD (<8%), LVMI (>125 g/cm^2) and IMT (>.75 mm) was present in 64 patients (90%): Figure.



Patients with echographic abnormalities.

Conclusion: In clinically uncomplicated essential hypertensives, metabolic insulin resistance is not associated with left ventricular hypertrophy, brachial artery endothelial dysfunction and/or increased carotid intima-media thickness. Integrated noninvasive ultrasound evaluation provides an accurate identification of incipient atherosclerotic damage - otherwise missed by conventional clinical and metabolic assessment.

P1005 High dosage of atorvastatin strongly reduces CRP within four weeks in diabetes mellitus; less marked effect on other inflammatory markers

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Inflammation is thought to play a role in the development and progression of atherosclerosis.
Three strong acute phase proteins, high-sensitive CRP (hs-CRP), serum amyloid A (SAA), secretory phospholipase A2 (sPLA2) as well as the cytokines interleukin-6 (Il-6) and TNF-a have emerged as prognostic inflammation markers for cardiovascular disease. Statin therapy has repeatedly been shown to reduce hs-CRP levels; the effects on the other markers are less well documented.
In a placebo-controlled trial the effect of 10mg and 80mg atorvastatin on the inflammation markers hs CRP, SAA, sPLA2 and IL-6 was measured after 30 weeks of treatment in 196 patients with type 2 diabetes and without manifest cardiovascular disease. In addition the effect on hs-CRP was followed after 4, 10 and 20 weeks. Ten patients with a baseline or follow-up hs-CRP level over 15 mg/L were excluded. The levels of the markers before treatment were found to be high and to correlate mutually. The correlations with CRP showed r= 0.411-0.600; Spearman p< 0.001.
hs-CRP, SAA, sPLA2, Il-6 levels were reduced by 15% (p=0.012), 8% (n.s.), 3% (p=0.040), and 3% (n.s.) (medians, Mann-Whitney) respectively in patients randomized to 10mg atorvastatin, and by 47% (p<0.001), 18% (p=0.001), 10% (p= 0.004), and 10% (p=0.086) respectively in patients randomized to 80mg atorvastatin. Pretreatment levels of hs-CRP, SAA, sPLA2 and Il-6 were not related to the changes. The effects on hs-CRP were achieved in 4 weeks for low-dose and for > 75% for high-dose atorvastatin relative to the follow-up at 20 and 30 weeks. The effects on hs-CRP of 80mg atorvastatin were present with all continued antidiabetic co-medication.
It is concluded that the anti-inflammatory effect of 80mg atorvastatin is achieved rapidly and is predominantly targeted at CRP, suggesting a specific anti-inflammatory effect.

P1006 Do all classical cardiovascular risk factors have the same impact in C-reactive protein plasma concentration in acute coronary syndromes?

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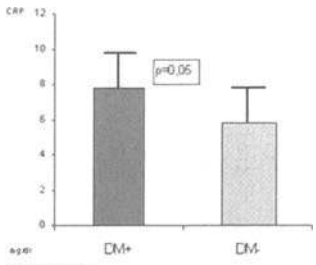
Elevated plasma concentration of C-reactive protein (CRP) is associated with increased global cardiovascular risk. We evaluated the influence of classical coronary heart disease risk factors (RF): hypertension (HT), smoking (SK), diabetes mellitus (DM), hypercholesterolemia (HC) and obesity (OB) in the level of CRP measured in acute myocardial infarction or unstable angina patients (pt). High-sensitivity CRP levels (Dade Behring test) were obtained upon entrance in 151 pts, 48 female, aged 65±12 years old, admitted within a 3-month period in the CCU. According to the presence of a single specific RF the whole of pts were divided in 2 groups: HT+ versus HT-, SK+ versus SK-, DM+ versus DM-, HC+ versus HC- and OB+ versus OB- and their CRP values compared (t-student and proportions comparison). The RF combination was also tested (RF<1 versus RF>2 up to RF<4 versus RF>5), in order to establish if the association of RF would impact on CRP and at wich level would it occur. HT+ was found in 64% of pts, SK+ in 25%, DM+ in 21%, HC+ in 34% and OB+ in 27%. CRP elevation was present in 83% of pts. A significant difference (p=0.05) was found only for pts with DM+ and DM-. In these subgroups, a significant difference was also found for the angiographic disease extension: multivessel disease in 89% of DM+ versus 46% in DM- (p=0.04) pts. We did not find a significant cut-off point for the association of RF. The presence of diabetes mellitus is associated with higher CRP serum levels in acute coronary syndromes.



CRP and DM.

This finding reflects the greater involvment of the coronary atherosclerotic process commonly associated with this metabolic condition. There was no association between this particular inflammatory marker, CRP, and any other RF or to their combination.

P1007 Silent myocardial ischaemia in diabetes mellitus: usefulness of adenosine ^{99m}Tc tetrofosmin myocardial SPECT

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Myocardial ischemia may not manifest symptoms in diabetic patients. The objective of this study was to evaluate if adenosine TC 99m tetrofosmin myocardial single photon emission tomography (SPECT) might detect silent myocardial ischemia in asymptomatic type 2 diabetic patients at high risk for coronary artery disease (CAD).

Methods: Fifty-seven patients (40 males, age 62,2 ys) with history of type 2 diabetes mellitus lasting more than 5 ys, unable to perform a standard stress test and presenting at least one of the following conditions (diabetic nephropathy or neuropathy, peripheral or carotid artery disease, elevated microalbuminuria) were enrolled in the study. All patients underwent adenosine-rest TC99 SPECT in a double-day protocol. Dividing the left ventricle in 20 segments, summed rest score (SRS), summed stress score (SSS) and summed difference score (SDS) were obtained with a 5-point scale (from 0=normal uptake to 4=absent uptake) by two operators. A gate-SPECT analysis was always provided. Silent myocardial ischemia was diagnosed when SDS>1; diabetic patients with extensive inducible ischemia (SDS>=3) underwent coronary angiography.

Results: In thirty-two (56.1%) subjects myocardial SPECT was normal; 25 (43.9%) showed silent ischemia, 16 (28.1%) of which had a SDS>=3. Coronary angiography was performed in all subjects with SDS>=3. A normal angiogram was found in 5 (31.2%), single-vessel disease in 2 (12.5%), two-vessel disease in 6 (37.5%) and three-vessel in 3 (18.8%). Three patients were treated with surgical revascularization and 3 with coronary angioplasty. At univariate analysis pts with more extensive silent ischemia had longer duration of diabetes (16.2±8.1 ys vs 11.8±5.8 ys, p=0.03), lower left ventricular ejection fraction (LVEF) at Gated acquisition after the adenosine infusion (44±11% vs 52.3±11.4%, p=0.03) and blunted reduction of diastolic blood pressure during the adenosine test (84.6±21.7 mmHg vs 75.3±7.2 mmHg; p=0.02). No differences were found in the metabolic control (glycosylated haemoglobin p=0.3, C peptide p=0.1) and lipid profile (triglycerides p=0.7; LDL cholesterol p=0.8).

Conclusion: adenosine TC99 tetrofosmin SPECT revealed myocardial ischemia in 43.9% totally asymptomatic diabetic pts. In pts with more extensive inducible ischemia angiography demonstrated CAD in 68.7%. The metabolic and lipid parameters were not different according to the degree of inducible ischemia.

P1008 How does the primary PTCA affects the long-term prognosis of diabetic patients?

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Objectives: to investigate feasibility and safety of primary PTCA in diabetic patients.

Background: diabetic patients with acute myocardial infarction (AMI) have been shown to be at high risk for adverse clinical outcomes. Limited data is available on long term prognosis of diabetics treated with primary PTCA.

Methods: retrospective analysis and follow up of consecutive 67 diabetic patients and 211 non diabetic patients treated with primary PTCA from 1/95 to 12/99.

Results: The baseline characteristics were comparable in both groups. The mean age was 62 years in diabetic patients and 59 years in non diabetic patients. Hypertension (49% vs. 36% p=0,05), contraindications to trombolytic treatment (13,4% vs. 5,7%, p=0,037), cardiogenic shock (16,4% vs. 7,1%, p=0,023), multivessel disease (34%vs 23%, p=0,07) and longer time delay to treatment (240 vs. 180 min, p=0,05) were more often present in diabetic group. 47% of diabetic and 42% of nondiabetic patients received stents. The TIMI 2 and 3 flow rates were reached in 91% of diabetic patients and in 89,1% of nondiabetic patients, but TIMI 2 flow was found more often in diabetics (11,9% vs. 3,3%, p=0,06). Diabetics had lower need for cardiopulmonal resuscitation during PTCA (0% vs. 5,2%, p=0,05) and higher rate of bleeding complications leading to significant change in the blood count (7,5% vs 1,4%, p= 0,01). Acute and subacute closure of infarct related artery and nonfatal reinfarction occurred in 3% vs. 3,3%, 3 vs. 0,9% and 1,9% vs. 3% in diabetics and nondiabetics respectively. Left ventricle ejection fraction 3-5 days after AMI was 47% in both groups. Higher 30 day mortality (11,9% vs. 5,2%, p= 0,05) was observed in diabetic group. However when the shock patients were excluded from the analysis, the 30 day mortality was comparable in both groups (4,5% vs. 2,4%, p=0,369). During 38+12 month follow up of 259 acute phase survivors 24 patients died, mortality in diabetics and nondiabetics was 11,9% vs. 8,5%(p=0,43), nonfatal reinfarction rate was 11,9% vs. 4,5% (p=0,039) respectively.

Conclusion: Primary PTCA seems to be safe and effective treatment of diabetic patients presenting with AMI. The prognosis of this high risk population however remains serious. Higher rate of bleeding complications at puncture site after PTCA can be explained by the lower quality of vessel wall in diabetic patients.

P1009 C-reactive protein may have a different prognostic value in diabetics and in non-diabetics patients with unstable angina

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Background: Diabetes is a pro-atherosclerotic and potentially pro-inflammatory condition associated with increased cardiovascular risk, yet no study has so far assessed whether the prognostic role of C-Reactive Protein (CRP) is different in diabetic and non-diabetic patients.

Methods: We assessed the prognostic role of CRP for in hospital death and myocardial infarction in 253 consecutive pts admitted to our CCU with a diagnosis of unstable angina. In all pts CRP was measured on admission by a nephelometric method (Dade-Behring). The data were evaluated by CRP quintiles.

Results: 200 pts were diabetics, 53 non-diabetics, in the overall population we observed 21 events (death+infarction), that were significantly more frequent in the top quintile (>19.8 mg/L) of CRP (P for trend =0.0019). More events were observed in diabetics (13% vs 7.5%), although the difference was not significant, CRP levels on admission were similar between diabetics and non-diabetics (respectively 4.5 mg/L range 0.35-144 and 5.21, range 0.2-188 mg/L, P=ns). However the prognostic role of CRP was significantly different between diabetics and non diabetics. In non diabetics 71% of events were concentrated in top quintile (10/14, P for trend <0.0001) but no differences in event rate was observed among CRP quintiles in diabetics.

Conclusions: our data support the role of CRP as an important unfavourable short-term prognostic factor in pts with unstable angina. However, in our study the prognostic role of CRP seems to be confined to non-diabetic pts. Other mechanisms of instability, such as extent and severity of coronary atherosclerosis and a pro-thrombotic state, might obscure the prognostic role of CRP in diabetic patients with unstable angina.

P1010 Inhibition of the renin-angiotensin system regulates the anti-inflammatory response of statins and aspirin in coronary artery disease

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Background: The therapeutic use of renin-angiotensin system (RAS) inhibitors results in a significant reduction of cardiovascular events in patients with coronary artery disease. Recent outcome studies demonstrate that these agents may have vascular benefits independent of blood pressure reduction. The addition of these agents to aspirin and statin therapy may provide additive or synergistic effects in reducing vascular pro-inflammatory and oxidative mechanisms.
Methods: We followed 124 normotensive patients with documented coronary atherosclerosis (pre-statin). These subjects were initiated on aspirin and atorvastatin to a low density lipoprotein (LDL) cholesterol of less than 100 mg/dl (post-statin) and then randomized to either the angiotensin converting enzyme inhibitor quinapril (QUI, 20 mg/day, n=69) or the angiotensin type 1 receptor antagonist irbesartan (IRB, 150 mg/day, n=55) for 8 weeks.
Results: In addition to the reduction of LDL cholesterol, atorvastatin reduced sP-selectin by 40 percent (0.57±0.08 to 0.38±0.06 ng/dl, $p<0.05$ from pre-statin), IL-6 by 18 percent (480±51 to 399±48 ng/dl, $p<0.05$ from pre-statin), and monocyte binding by 13 percent (90±11 to 76±18 percent of monocytes binding to the CD11b antibody, NS). The addition of either QUI or IRB further reduced sIL-6 (QUI, 330±51; IRB, 301±48 ng/dl, $p<0.05$ from pre- and post-statin). Furthermore, there was a profound decrease in monocyte binding in patients placed on either RAS inhibitor (QUI, 33±10; IRB, 27±6 percent of monocytes binding to the CD11b antibody, $p<0.05$ from pre- and post-statin). Both QUI and IRB were well-tolerated by the treatment groups and did not cause any significant hypotension in the normotensive population with coronary artery disease.
Conclusions: Our findings indicate that the addition of RAS inhibitors to aspirin and statin therapy differentially regulate markers of inflammation and oxidation in the vasculature and may demonstrate potential mechanisms by which these agents are effective in the secondary prevention of coronary atherosclerosis.

CARDIOVASCULAR CONTROL MECHANISMS IN HEALTH AND DISEASE

P1011 Effects of intensive resistance training on isotonic exercise Doppler indexes of left ventricular systolic function

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Background: Endurance (isotonic) and resistance (isometric) training programs are known to induce different cardiovascular adaptations. It is still unclear whether resistance athletes may have an improved cardiocirculatory response to endurance exercise. The aim of this study was to evaluate Doppler-derived indexes of left ventricular (LV) systolic function during isotonic exercise in a highly trained population of resistance athletes, in comparison to age- and gender-matched endurance athletes and sedentary individuals.
Methods: Doppler echocardiography at rest and at supine symptom-limited isotonic exercise was performed in 120 male subjects: 40 weightlifters (mean age 29±4), 46 long-distance runners (mean age 29±6; p=NS) and 34 healthy sedentary men (mean age 30±5; p=NS).
Results: At peak exercise stroke volume increased by 65% above rest values in runners, by 77% in weightlifters ($p<0.05$) and by 37% in sedentary ($p<0.0001$ vs. athletes), associated with a parallel increase in end-diastolic volumes. The volumetric changes led to an increase in LV ejection fraction, from 64±7 to 92±7 in runners, 69±8 to 92±6 in weightlifters, and 67±7 to 86±6 in sedentary ($p<0.05$ vs. athletes). Peak flow velocity was 119±15 in runners, 114±12 in weightlifters, and 102±9 cm/s in sedentary ($p<0.05$ vs. athletes), increasing to 213±19, 203±16 and 160±14, respectively, at exercise ($p<0.0001$ vs. athletes). No significant rest or exercise differences were documented between both athletes groups. Mean acceleration values were higher for the runners and the weightlifters: 14.2±1.3 and 13.7±1.2 m/s/s, respectively, vs. 12.2±1.1 in sedentary ($p<0.01$). During exercise, a sharp increase to 39.3±5 and 37.3±4, respectively, was seen in the athletes (p=NS), and a less pronounced one to 25.4±2.5 in the sedentary ($p<0.0001$).
Conclusions: Two major findings can be drawn from the present study. First, resistance-trained athletes show an improved cardiovascular response to isotonic exercise, as reflected by Doppler-derived indexes of aortic flow (peak flow velocity and mean acceleration) compared to sedentary men, notwithstanding the fact that these athletes lacked of previous conditioning with this specific type of exercise. Second, the LV response to isotonic exercise in resistance athletes does not appear to be different than in endurance athletes.

P1012 Abnormalities in myocardial contractility, metabolism and perfusion reserve in non-stenotic coronary segments in heart failure patients

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Objective: Myocardial blood flow (MBF) reserve is impaired in congestive heart failure (CHF), while fluorine-18-deoxyglucose (18FDG) uptake is relatively preserved. To determine whether this mismatch could be interpreted as ischemia, we performed dobutamine stress echocardiography (DSE).
Methods: 12 males with coronary artery disease (CAD) and CHF were compared with 12 controls with similar CAD but normal left ventricular (LV) function. MBF in non infarct-related artery areas was assessed using N13-ammonia positron emission tomography (PET), at rest and after dipyridamole infusion and 18FDG-uptake was determined. DSE was performed with doses up to 40 μg/kg/min.
Results: In areas with non-stenotic arteries MBF-reserve was more impaired in CHF patients (1.6±0.6 vs. 2.2±0.5; CHF vs. normal LV resp. $p<0.05$). MBF-reserve was related to LV ejection fraction ($r=0.6$, $p<0.05$) and wall stress ($r=-0.72$, $p<0.05$). PET showed mismatch in 4±1% of the myocardium in normal LV, compared to 26±26% in CHF ($p<0.05$), coinciding with more ischemic wall motion abnormalities on DSE (21% vs 4%; CHF vs. normal LV resp, $p<0.05$).
Conclusions: In CHF, mismatch was found in areas supplied by non-stenotic coronary arteries. Correponding areas showed ischemic wall motions on DSE. These findings suggest that the condition of CHF may play a role in perpetuating myocardial failure by inducing myocardial ischemia. Follow-up studies to investigate the ischemia-CHF relationship in time would be needed.

P1013 The role of cardiac power and systemic vascular resistance in the pathophysiology and diagnosis of patients with acute congestive heart failure

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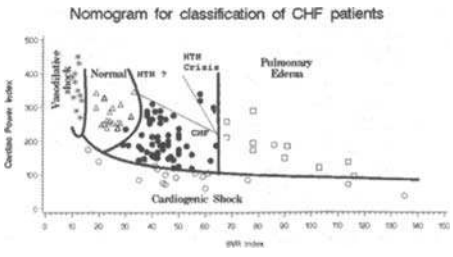
Conventional hemodynamic indexes (cardiac index (CI), and pulmonary capillary wedge pressure) have previously demonstrated only limited value in the diagnosis and treatment of patients with acute congestive heart failure (CHF).
Methods: We have measured CI, wedge pressure, right atrial pressure (RAP) and mean arterial blood pressure (MAP) in 89 consecutive patients admitted due to acute CHF (exacerbated systolic CHF (n=56), hypertensive crisis (n=5), pulmonary edema (n=11) and cardiogenic shock (n=17)) and in two control groups: Eleven patients with septic shock and 20 healthy volunteers. Systemic vascular resistance index (SVRi) = (MAP-RAP)/CI. Cardiac contractility was estimated by the cardiac power index (Cpi), calculated as CI x MAP.
Result: We have found that CI < 2.7 Lit/min/M2 and wedge pressure > 12 mmHg are universally measured in patients with acute CHF. However these measures are often overlapping among patients with the above-mentioned different syndromes of acute CHF, while Cpi and SVRi are significantly different. Cpi was low in patients with exacerbated CHF and extremely low in patients with cardiogenic shock while SVRi was increased in patients with exacerbated systolic CHF and extremely high in patients with pulmonary edema. By using a two-dimensional presentation of Cpi versus SVRi we have found that these clinical syndromes can be accurately differentiated, as the paired measurements of each clinical group segregated into a specific region on the Cpi/SVRi normogram, that could be mathematically defined by a statistically significant line (Figure, Lambda=0.95).



Conclusion: Measurement of SVRi and Cpi and their two-dimensional graphic presentation enables accurate diagnosis and follow up of individual patients with acute CHF.

P1014 Intrapatient observations of autonomic nervous system activity during spontaneus and angioplasty coronary ischaemia

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Although autonomic sympatho-vagal balance has been reported to be abnormal in pts with anginal syndromes, it is still not known whether this abnormality may concur to the development of coronary occlusion in the natural history of the disease. Alternatively it could simply be an expression of the interaction between pain perception, coronary occlusion and neural reflexes.

Methods: To address this topic we studied 40 pts admitted to CCU for unstable angina, candidates to revascularization by PTCA in single vessel disease. All pts had > 75% stenosis of the left anterior descending coronary artery. ECG Holter monitoring was performed in all pts starting 2 to 6 hours before cardiac catheterization. Frequency domain measures of heart rate variability were assessed by power spectral analysis during spontaneous or balloon induced ischemia, and 1 to 5 min. before and after the ischemic episodes. Low (LF: 0.04-0.15 Hz) and high frequencies (HF:0.15-0.40 Hz) were assumed to be the expression of sympathetic and parasympathetic activity, respectively. LF/HF ratio was used to estimate the overall autonomic nervous system balance.

Results: Eight of the 40 pts experienced spontaneous ischemia during cardiac catheterization just before angioplasty. Angiography during spontaneous episodes showed transient total or subtotal coronary occlusion. Hundred episodes were analysed: 78 secondary to balloon obstruction and 22 spontaneously occurring. LF/HF ratio was dramatically reduced during balloon induced ischemia as compared to values recorded 5 min. before (0.5 ± 0.7 vs 3.7 ± 2.1, p< 0.01). The opposite occurred during spontaneous ischemia (12 ± 6.5 vs 4.3 ± 2.6, p<0.01). Spontaneous ischemic episodes were longer than those provoked by balloon angioplasty (180 ± 90 vs 120 ± 60 sec).

Conclusions: 1) A shift in the autonomic nervous system balance towards sympathetic activation may be a factor concurring to cause spontaneous coronary occlusion in unstable angina. 2) The hypothesis that neural reflexes originating by coronary occlusion itself, or by chest pain could trigger increased sympathetic activity during unstable angina, appears to be unlikely.

P1015 Adenosine and endogenous opioid sensitivity in patients with silent myocardial ischaemia and angina pectoris

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Introduction: Different studies have shown that patients with silent myocardial ischemia (SMI) have the same prognosis as patients with angina pectoris (AP), despite this fact, they make much fewer primary and emergency visits. The aim of the present investigation was to study the differences in tolerability of the ischemic pain messenger, adenosine (ADO), in patients with AP, SMI and to healthy volunteers and study the effect of non-selective opioid antagonism on adenosine provoked pain.

Method: 13 patients with SMI (mean age 58±10 with BMI 25± 3) who underwent examination with exercise stress test or myocardial scintigraphy, with ECG ischemic changes and no pain during the test were compared with 10 patients with AP (mean age 57±9 with BMI 29±5) and positive test. Significant stenosis in one or several coronary vessels were shown during coronary angiography. Both groups were compared to a group of healthy volunteers (mean age 49±2 with BMI 26±4) n=10. The subjects received increasing doses of adenosine injected rapidly into antebrachial vein to estimate maximum tolerable dose (MTD). Initial dose was 2.5 mg, which was increased in steps of 2,5 mg. 1 minute after each dose of adenosine central chest pain was quantified using 0-10 point scale of Borg. When the MTD of adenosine was titrated, the subjects were given 4 doses (placebo, 1/3, 2/3, 3/3 of MTD) of ADO in double-blind random order. This was repeated double-blind after injection of a non-selective opioid antagonist (naloxone 0.4 mg/ml 1ml).

Results: Patients with SMI showed a higher pain threshold compared to the AP group (pain duration p=0,001), (pain area p=0,004), (Borg p=0,023) at 1/3 and 2/3 of MTD and this difference was abolished by naloxone. The same pattern of altered pain perception was seen in the SMI group compared to healthy volunteers without any effect after naloxone injection (pain duration p=0,027). There was an increase in pain within healthy and the SMI group after naloxone injection compared to before (p<0,05).

Conclusions: A decreased pain sensitivity to adenosine was evident in patients SMI compared to patients with AP. The lower pain in the SMI group disappeared after injection of naloxone. Naloxone decreased pain threshold in healthy and SMI group (p<0,05). Our results clearly suggest a role of peripheral endogenous opioid receptors in perception of pain, particulary in low grade pain among patients with SMI.

Key words: Silent myocardial ischemia, Angina pectoris, Adenosine, Maximal tolerable dose

P1016 Optimal oxygenation is important in patients receiving dobutamine because this drug markedly enhances chemoreflex sensitivity to hypoxemia

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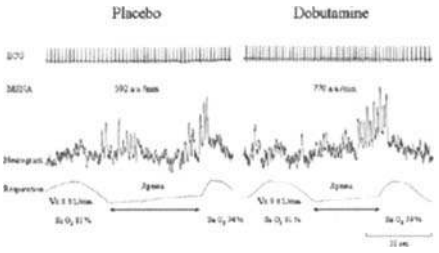
Background: There is evidence that beta-adrenergic mimetic agents may increase chemoreflex sensitivity to hypoxemia in humans. Whether this occurs also with the beta-1 adrenergic mimetic agent dobutamine, which is frequently administered to patients with heart failure, is not known.

Methods: We tested the hypothesis that dobutamine (5 μg/kg/min) increases chemoreflex sensitivity in 15 normal humans in a randomized, double-blinded, placebo-controlled study. We examined the effects of dobutamine on the respiratory, cardiovascular and sympathetic nerve activity (SNA, microneurographic technique) during normoxia, isocapnic hypoxia (10% O2 in 90% N2), maximal voluntary end-expiratory apnea and hyperoxia.

Results: Dobutamine markedly increased the ventilatory response (16.1±1.6 vs. 11.4±0.7 L/min at the 5th min of hypoxia, ANOVA p<0.0001) and the SNA response to isocapnic hypoxemia (403±94 vs. 222±5% at the 5th minute of hypoxia, ANOVA p<0.03). Peripheral chemoreflex deactivation by hyperoxia suppressed these effects (ventilation: 8.4±0.5 vs. 7.9±0.6 L/min, p=NS). Moreover, the apneas at the end of hypoxia which were performed with dobutamine were shorter than those under placebo (17±2 vs. 19±1 sec, p=0.01, Figure 1) and were accompanied by larger increases in SNA (501±107% vs. 291±38% with placebo, p<0.05) despite a lower reduction in oxygen saturation (81±2% with dobutamine vs. 77±1% with placebo, p<0.05).



Conclusions: Marked increases in the ventilatory and sympathetic response to hypoxemia reveal that dobutamine enhances peripheral chemoreflex sensitivity. Clinicians should be aware of this effect and attempt to maintain optimal oxygenation in patients with heart failure receiving dobutamine.

P1017 Vascular effects of L-NMMA are mediated via actions on eNOS not L-arginine transport

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Background: Impaired endothelial function is well established in congestive heart failure (CHF), on the basis of decreased responses to both agonist-induced and shear stress stimuli. The downregulation of eNOS expression and activity has been proposed as a mechanism for this defect. We recently identified a decrease in L-arginine (L-arg) transport in the forearm, suggesting that substrate limitation may also contribute. To further investigate this abnormality, we determined the effect of L-NMMA on both blood flow and L-arg transport in control (C) and congestive heart failure (CHF) patients.

Methods and Results: Measures of L-arg transport ([3H]L-Arg clearance) and endothelial function (venous occlusion plethysmography) were performed in 19 male NYHA class II/III CHF pts (age 54 ± 3 years) and 17 healthy male volunteers (CON; age 53 ± 3 years). Forearm blood flow (FBF) responses to intra-arterial ACh infusions were attenuated in the CHF pts (37 μg/min, 6.26 ± 0.88 ml/min/100ml) when compared to the C group (37 μg/min, 11.6 ± 1.41 ml/min/100ml; p=0.01), while basal blood flow was similar between the two groups (p=ns). We next evaluated the effect of intra-arterial L-NMMA, an inhibitor of eNOS which also inhibits L-arg transport. L-NMMA reduced FBF in both C (4 μg/min, -1.43 ± 0.31 ml/min/100ml; p=0.003) and CHF pts (4 μg/min, -0.42 ± 0.13 ml/min/100ml; p=0.003), and the change in blood flow was significantly greater in C vs. CHF (p=0.001). At baseline, L-arg transport was greater in C (111.96 ± 9.77 ml/min) than CHF pts (84.27 ± 9.04 ml/min; p=0.05). L-arg transport was reduced to the same extent following L-NMMA infusions (C vs. CHF; -22.71 ± 5.33 vs -25.71 ± 6.22%; p=ns).

Conclusion: The present study confirms our earlier finding of reduced L-arg transport as a potential mediator of impaired endothelial function in CHF. Our observation that L-NMMA produces a greater blood flow reduction in C than in CHF, while exerting similar effects on L-arginine transport suggests that this agent acts principally to inhibit eNOS rather than L-arg transport.

INFLAMMATORY MECHANISMS OF CELL DAMAGE

P1018 Role for a novel integrin linked kinase in leukocyte recruitment

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Chemokines such as MCP-1 are potent monocyte agonists and a growing body of evidence from animal models and human specimens suggest a key role in the pathogenesis of atherosclerosis. Chemokines modulate monocyte integrin avidity to coordinate adhesion and subsequent transendothelial migration, though the sequential signaling pathways involved remain poorly characterized. Here we show that integrin linked kinase (ILK), a recently described 59-kDa serine-threonine protein kinase which interacts principally with beta1-integrins, is highly expressed in human mononuclear cells and has sustained activation by exposure of leukocytes to the chemokine MCP-1. Biochemical inhibitor studies show that chemokine-triggered activation of ILK is downstream of phosphoinositide 3-kinase (PI 3-K). In functional assays in a parallel plate laminar flow chamber (2,0 dynes/cm^2), overexpression of wild type ILK in human monocytic cells markedly diminishes beta1-integrin/vascular cell adhesion molecule-1 (VCAM-1)-dependent firm adhesion to human endothelial cells [13.2± 1.0 (Control transduced) vs. 2.6±1.1 (ILK transduced), $p<0.001$]. These data implicate ILK in the dynamic signaling events involved in the regulation of monocyte integrin avidity for endothelial substrates, potentially in the transition from stable arrest to subsequent migration. Identification of the signaling pathways responsible for monocyte recruitment could provide further insights into celluar mechanisms underlying human atherosclerosis and potentially identify new targets for therapeutic intervention.

P1019 High dose of aspirin inhibits NF-kB and protects against endorgn damage in rats with human renin and angiotensinogen genes

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Recently, it was reported that aspirin (ASA) inhibits I-kB kinase beta in vitro. We previously showed that NF-kB activation and inflammation plays a crucial role in the pathogenesis of dTGR. We now tested the hypothesis that ASA inhibits NF-kB and ameliorates renal and cardiac end-organ damage. The dTGR feature hypertension, severe renal and cardiac damage. We treated rats chronically with ASA (600 and 25 mg/kg ip). Only apirin 600 prevented mortality, while untreated dTGR and ASA 25 showed mortality > 50% at 7 weeks. ASA 600 reduced cardiac hypertrophy (4.0±0.2 vs. 5.7±0.2 mg/g, $p<0.001$) compared to dTGR. Blood pressure levels in ASA 600 were slightly, but not significantly lower (158±8 vs. 182±8 mm Hg, p=0.2). In contrast, ASA 600 reduced albuminuria by 85% ($p<0.01$) and perivascular fibrosis. However, apirin 25 had no effect on cardiac and renal damage. ASA 600 inhibited renal I-kB kinase activity and NF-kB DNA binding activity, which was increased in dTGR. Immunohistochemical analysis shows increased expression of the activated p65 NF-kB subunit in the endothelium, smooth muscles cells, infiltrated cells, glomeruli, tubuli of dTGR, which was markedly reduced by ASA 600. ASA 600 also resulted in reduced immunostaining of NF-kB-regulated genes laminin, ICAM-1 and IL-6. Monocyte infiltration was increased in dTGR hearts and kidneys and reduced by ASA 600, and not by ASA 25. Thus, these results demonstrate that only high dose ASA inhibits NF-kB, suppresses inflammation and protects against ANG II-induced end-organ damage.

P1020 Evaluation of the phasic variation of monocyte membrane markers during acute coronary syndromes

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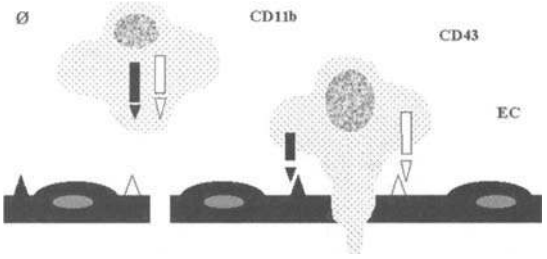
In acute coronary syndromes (ACS) an inflammatory response (IR) is associated with the instability of the coronary artery plaque related to the activity of the monocyte (M) type cell involved. Our aim was to analyse the time variability of several M cell membrane markers (MM) during the first days post ACS. We studied a group of 52 ACS pts, aged 65±12 yrs, 69% male, after CCU admission. Blood samples were collected in EDTA at day 1, 3, 5 and 10 post admission and after discharge. The absolute and relative M circulating levels (n-%/mm^3), and its relative % to blood white cells count (%M-%) were determined. After a selective M cell MM process, a quantitative flow citometry method was applied to assess the concentration of M MM/mm^3, ICAM and VCAM ligands such as CD11b and CD43 and its ratio CD11b/CD43. We also evaluated the levels of fibrinogen (FB-mg/dl), mioglobin (MG-U/L), C-reactive protein (CRP-mg/dl), troponin I (TI-μ/L), total CK (U/L) and CK-MB (U/L) isoenzyme. Between day 1 and 10 post ACS, the CD11b levels suffered a significant variation of +13.5% (130.6-148.3/mm^3) with a peak level at day 5, CD43 registered higher initials levels and a variation of +7.3% (39.5-24.1/mm^3) with a peak at day 3, and CD11b/CD43 ratio a variation of +31% (3.07-5.02; $p<0.01$) with a correspondent peak at day 5. The CD11b/CD43 ratio registered also significant correlations with the CRP levels (r=0.55; $p<0.01$), troponin I (r=0.37; p=0.02) and total CK (r=0.40; p=0.02), different from the other variables. The MM suffer a variation during the acute phase of the myocardial ischemic ACS process.



The phasic variation of these M cell MM reflect the intensity of the IR associated with plaque instability and may correspond to a cell index of the myocardial inflammation level in acute ischemiaMonocyte receptors

P1021 Atorvastatin decreases the upregulation of COX-2 and EP1 receptor induced by proinflammatory cytokines in cultured vascular smooth muscle cells

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Background: Inflammation constitutes a key factor in the initiation, progression and rupture of the atherosclerotic plaque. One enzyme implicated in the inflammation is cyclooxygenase 2 (COX-2), not constitutively expressed in normal vessels. COX-2 is responsible for the synthesis of proinflammatory prostaglandins (PGs) such as PGE2, which exerts a wide variety of actions through G protein –coupled receptors (EP 1- 4). Little is known, however about the regulation of the EPs in atherosclerosis. In addition, recent data have shown some antiinflammatory effects of HMG-CoA reductase inhibitors (statins). The aim of this work was to study the expression of COX-2 and of different PGE2 receptors in vascular smooth muscle cells (VSMC) induced by proinflammatory cytokines such as IL-1beta and TNF-alfa, as well as its modulation by atorvastatin (Atv).

Methods and Results: mRNA expression of COX-2, EP1, EP2 and EP-4 receptors induced by TNF-alfa and IL1-beta (100U/ml, each) was studied in rat VSMC by RT-PCR. Stimulation with cytokines elicited an increase of COX-2 expression (3.2±1 fold). EP-1 receptor expression was induced at 3h (2.3±2 fold), diminished at 6h, increased again at 8h (1.8±0.8 fold; and 4.1±5 fold, respectively) and kept constant until 24h. The expression of EP-4 receptor peaked at 8 h. However the expression of EP-2 and COX-1 remained invariable with the time. Since it has been suggested that Atv may have antiinflammatory effects, additional experiments were performed. Preincubation for 1 h with Atv (10^{-5} M) significantly reduced COX-2 expression at 8h (1.0±0.8 fold, 56%) coinciding with a reduction in the expression of EP1 (0.8±0.5 fold, 75%). Antiinflammatory compounds such as acetylsalicylic acid (100μM) and dexamethasone (1μM) significantly decreased the expression of COX-2 and EP1 at both 3 and 8h. Comparatively, the reduction obtained with Atv was slightly lower to that observed with the antiinflammatory drugs (76-91%). In addition, pyrrolidine dithiocarbamate (200μM), a known NF-kB inhibitor and antioxidant, diminished the COX-2 and EP1 mRNA expression, suggesting the implication of this nuclear factor.

Conclusions: In cultured VSMC, proinflammatory cytokines such as TNF-alfa and IL1-beta upregulate the expression of COX-2 and several PGE2 receptors. This effect was reduced by Atv in the range obtained by classical antiinflammatory drugs, probably via NF-kB. These data further support the antiinflammatory properties of Atv.

P1022 Application of TNF receptor ameliorates cardiac and renal end-organ damage in Ang II-dependent hypertension independent of blood pressure

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We recently reported that rats harboring both human renin and angiotensinogen genes (dTGR) feature moderate hypertension, severe renal and cardiac damage, and a 50% mortality at 7 weeks. We also showed that TNFa is increased in both hearts and kidney by western blot and immunohistochemisty in this model of angiotensin II (Ang II) induced end-organ failure. Rats over expressing TNFa develop chronic heart failure associated with severe leukocyte infiltration in both the atria and the ventricles. Moreover chronic treatment with a soluble TNFa receptor (sTNF-R) in patients with heart failure resulted in a significant dose-dependent improvement in LV structure and function and a trend toward improvement in patient functional status. Thus, we tested the hypothesis that TNF signaling is involved in Ang II-induced cardiac and renal damage. We treated rats chronically with sTNF- for 3 weeks. sTNF-R had no effect on blood pressure (211±8 vs. 194±7 mm Hg, Sprague Dawley rats (SD): 110±1 mm Hg), however cardiac hypertrophy index was reduced (5.64±0.13 vs. 4.75±0.09 mg/g, $p<0.05$, SD: 3.5±0.05 mg/g) compared to dTGR. sTNF-R reduced 24 h albuminuria by 50% (37.3±8.1 vs. 16.9±3.2 mg/d, $p<0.05$, SD: 0.2±0.02 mg/d). Vasculopathy and perivascular cardiac fibrosis were markedly ameliorated by sTNF-R. Immunohistochemical analysis showed increased infiltration of monocytes and T-cells in dTGR which was significantly reduced by sTNF-R. sTNF-R was only partially effective in the kidney. Electrophoretic mobility shift assay showed increased NF-kB and AP-1 DNA binding activity in heart and kidney of dTGR. The DNA-binding activity of both transcription factors was reduced by sTNF-R in heart and kidney. Immunohistochemical analysis shows increased expression of the p65 NF-kB subunit in dTGR that was reduced by sTNF-R treatment. Similarly, immunohistochemistry showed that the TNF-regulated adhesion molecule ICAM-1 was reduced in heart in the sTNF-R treated compared to untreated dTGR. These results demonstrate that TNF signaling is involved in Ang II-mediated end-organ damage in vivo. Blocking TNFa signaling does not reduce Ang II induced hypertension in vivo. sTNF-R reduced NF-kB and AP-1 DNA binding activity and reduced cardiac damage independent of blood pressure.

P1023 Low molecular weight dextran sulfate acts as an endothelial cell-protectant and prevents complement activation in xenotransplantation models

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Introduction: The complement (C) system plays a critical role in the rejection of xenografted cells and organs as well as in the damage of endothelial cells (EC) as occurring e.g. during ischemia/reperfusion injury after myocardial infarction. Dextran sulfate of MW 5000 (DXS) is known to block C-activation and to regulate the coagulation cascade by potentiation of C1-inhibitor. Due to its negatively charged nature we hypothesized that DXS can bind to the endothelium and protect it from C-mediated damage.

Methods: A FACS assay using pig cells (PK15 as well as pig aortic EC) was developed to analyze C-deposition, DXS binding and cell survival. Pig cells were preincubated with DXS (0,04 to 25 mg/ml) for 30 minutes at 37°C, 5% CO2, followed by washing, and incubated with normal human serum (NHS) to induce C-mediated damage. The cellular localization of DXS was analyzed by confocal microscopy using a FITC labeled DXS (DXS-FITC) and also evaluated on more complex tissues like pieces of rat aorta in a setting of ischemia/reperfusion injury.

Results: DXS was able to inhibit human serum-mediated C deposition (C3c, C4c) on pig cells in a dose dependant manner (IC50 = 0,7 mg/ml). This cytoprotective effect was still present when the challenge with human serum was done up to 48 hours (IC50 = 18 mg/ml) after the 30 min incubation of the cells with DXS, followed by washing. Up to a concentration of 100 mg/ml, DXS had no toxic effects on the cells. By FACS analysis and confocal microscopy, we could show that cytoprotection was paralleled by binding of DXS-FITC, both to the cell surface and the nucleus.

Discussion: Our results indicate that DXS is able to bind to the endothelium and to protect it from C deposition mediated endothelial injury. These data suggest that DXS acts as an "endothelial cell protectant" with potential for clinical application to prevent ischemia/reperfusion injury after PTCA or cardiac surgery and heart transplantation.

IMAGING OF ATHEROSCLEROSIS

P1024 In vitro photodynamic diagnosis of atherosclerotic wall changes with use of mono-l-aspartyl chlorin e6

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Background: Although there are several methods for atherosclerosis detection available, none of them seems to be accurate enough to solve the problem. Photosensizer Assisted Light Induced Fluorescence (PALIF) as a background for photodynamic diagnosis (PDD) and therapy (PDT) is a new method based on using photosensitizing drugs and light of appropriate wavelength needed for drug activation. The aim of this study was to asses in vitro the capability of PALIF with use of chlorin e6 as a PS to recognize different stages of atherosclerosis and its usefulness as a feedback system for photoangioplasty treatment.

Methods: 20 specimens of human aorta and 10 specimens of human coronary artery from eight patients were obtained at autopsy. The patients ranged in age 45 to 76 years. The specimens were soaked with mono-l-aspartyl chlorin e6 for 15 minutes and then washed out. The luminescence spectra using 440 nm wavelength light from a Mercury lamp were collected and analyzed. Subsequently all specimens were histologically examined and basing on the pathological changes occurring in intima and media classified into three groups: 1: normal artery wall 2: atherosclerotic noncalcified plaque and 3: calcified plaque

Results: Tissue fluorescence is seen as green light with three peaks at 490, 515 and 543 nm, chlorin e6 fluorescence is seen as a fourth peak at 660 nm. Compared with the spectrum obtained from normal artery wall, spectra collected from noncalcified and calcified plaque show the reduction of green fluorescence intensity, with strongly reduced green part of the spectrum collected from noncalcified samples. Moreover we noted a very strong red fluorescence of chlorin e6 originating from lipid reach, noncalcified samples. We established a quantitive factor which is the ratio Re6 of chlorin e6 red intensity in its 660 nm maximum compared to the area of green luminescence centered at 516 nm. The highest value of the ratio was reached at atheromatous samples, then calcified and normal ones (R=3.53, R=1.63, R=1.50 respectively, $p<0.05$).

Conclusions: PS assisted spectroscopy can be a comparable, quantitive method of identifying artery wall changes. It may be a specific tool for atheromatous and normal or calcified segments discrimination. Further animal and clinical trials must be performed to evaluate in vivo atheroma detection algorithm as a feedback system for photoangioplasty. The advantage of the above method is a possibility of a real time imaging followed by targeted therapy of various forms and stages of atherosclerosis

P1025 Fusion imaging in chronic coronary artery stenosis by magnetic resonance phosphorus spectroscopy and 3D coronary angiography

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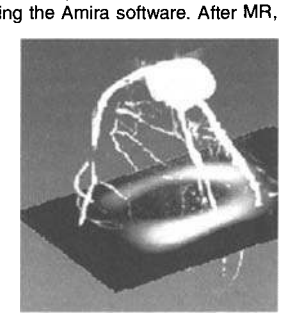
Aim of the study was to evaluate the concept of fusion imaging by magnetic resonance spectroscopy and imaging in the model of chronic coronary stenosis in the rat. 3D coronary angiograms were fused with ATP metabolite maps, which were acquired by 31P localized MR spectroscopy in the isolated rat heart.

Stenosis was induced by a ligation including a 300µm wire placed next to the left coronary artery. The wire was taken away imediately after the suture was closed. 2 weeks later localized 3D 31P Chemical Shift imaging was performed in 8 isolated perfused hearts on a Bruker 12 T AMX. (voxel size 4x4x6 mm). 1H gradient echo images were acquired to correlate position of the stenotic region in the metabolite maps and the angiography data, which was segmented and used for volume correction of spectroscopy. PCr/ATP was determined in a control and the ischemic region. MR angiography was performed with a flow weighted 3D gradient echo (TE 1.0ms, matrix 128±3). Metabolite maps of ATP were fused with the coronary angiogram using the Amira software. After MR, fraction of scarring within ischemic region was determined in histology. 3D MRA enabled detection of coronary stenosis. In the ischemic region, PCr/ATP was decreased when compared to control region (1.24 ± 0.38 vs 1.45 ± 0.49, $p < 0.05$). Fraction of fibrosis in histology was 12.81.4%, and correlated to ATP signal reduction in the ischemic region ($r = 0.71$, $p < 0.05$).

In future this kind of image fusion might be of help in fast characterisation of the severity of a stenosis and might aid decision making concerning revascularisation, because not only anatomy, but also metabolic information can be given at a glance.



Fusion image.

P1026 Non-invasive differentiation of plaque morphology using multi-slice computed tomography: experimental and post-mortem studies

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Background: Initial clinical results indicate that multi-slice computed tomography (MSCT) might be used for the non-invasive differentiation of human coronary plaque morphology by measuring plaque density. Aim of the present studies was a) to determine the reliability of this new methodology in post-mortem studies, and b) to evaluate influence factors on the density measurements
Methods: a) 10 human hearts were scanned post mortem, focusing on the presence of atherosclerotic coronary plaques. Density measurements were performed within these plaques, which were furthermore histopathologically classified according to the Stary classification.
b) A coronary phantom model was developed, consisting of silicon tubes (lumen diameter 4 mm), with two plaques of known density inside, simulating soft and intermediate lesions (plaque 1: -39 Hounsfield Units [HU], plaque 2: 72 HU). Density measurement were conducted in 3 different contrast media concentrations ([CMC], 1:30, 1:40, 1:50) All MSCT scans were performed on a Somatom Volume Zoom™ (Siemens, Forchheim, Germany).
Results: a) 13 plaques were detected by MSCT (n=4 soft [Stary III/IV], n=5 intermediate [Stary V], n=4 calcified [Stary VII]). Soft plaques had a mean density of 41±17 Hounsfield units (HU), intermediate plaques of 73±20 HU, and calcified plaques of 772±330 HU.
b) Both Plaques (P1/2) could be differentiated from each other on all three CMC. Rising CMC lead to significant higher density values within the plaques ($p<0,001$).
Conclusions: The post-mortem results confirm that human coronary plaque morphology might be reliably evaluated by the use of MSCT. However, when determining tissue density levels within small anatomic structures such intracoronary atherosclerotic plaques, partial volume effects have to be taken into account, affecting precision of the measurements. Our data indicate, that standardization of methodology is required, before it can be reliably applied in the clinical setting.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY VALVULAR HEART DISEASE

P1027 Is TEE necessary after a transthoracic echo negative for left atrial thrombi in atrial fibrillation in presence of severe mitral regurgitation

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Incidence of systemic embolism (SE) and thrombi (T) within the left atrium (LA) has been documented to be lower in pts with severe mitral regurgitation (MR) as compared to pts without MR despite comparable LA size and atrial fibrillation (AF). Although transesophageal echo(TTE) provides higher diagnostic performance than transthoracic echo(TTE) for LAT, indications of TEE for exclusion of LAT,and necessity of anticoagulation in pts with AF in presence of severe MR remain to be determined.We aimed to compare TTE and TEE in diagnosis of LAT in pts with AF associated with rheumatic mitral valve disease (RMVD),and to assess whether diagnostic performance of TTE for LAT relates to the presence of severe MR.The study group comprised 261 pts (M 176, F 85,mean age 41±16) with chronic AF and RMVD assessed by TTE and TEE before mitral valve surgery. Pure or predominant mitral stenosis (MS) was defined as mitral valve area <1.5 cm^2 and MR jet area <4 cm^2 (n= 91), severe MR was defined as jet area >8 cm^2 and/or jet area/ left atrial area $>40\%$ (n= 73), and MS concomitant with MR was defined as MS with MR jet area between 4 and 8 cm^2 (n=97). Echodensities mimicking LAT on 2D TTE study but remaining within the area of color flow MR jet were not accepted as LAT. Preop TTE and TEE diagnosed 15 and 44 out of the 46 LAT detected during operation, respectively. Incidence of LAT in pts with and without severe MR was 1.4% and 24% ($p<0.001$),respectively. For LAT, overall sensitivity of TTE and TEE was 34% and 95%, specificity was 96% and 94%, positive predictive value (PPV) was 80% and 89%, negative predictive value (NPV) was 75% and 97%, and diagnostic accuracy (DA) was 76% and 95%,respectively. In pts with and without severe MR, sensitivity of TTE was 100% and 33%, specificity was 98.5% and 95%, PPV was 50% and 85%, NPV was 100% and 64%, and DA was 97% and 67.5%, respectively. In pts with and without severe MR, sensitivity of TEE was 100% and 95%, specificity was 100% and 90%, PPV was 100% and 89%, NPV 100% and 96%, and DA was 100% and 92.5%,respectively.
Conclusions: Diagnostic performance of TTE for LAT in pts with rheumatic AF seems to be associated with type of RMVD,and color flow mapping on TTE study may be considered as reliable as TEE for exclusion of LAT in presence of severe MR.In a patient with TTE Doppler criteria of severe MR and negative for LAT, further TEE with this indication may not be necessary.

P1028 Importance of post-cardioversion transoesophageal echocardiography for the timing of anticoagulation in atrial fibrillation: a 1 year follow-up

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Background: In patients (pts) with atrial fibrillation (AF) recommended for electrical cardioversion (EC), the guided approach with transoesophageal echocardiography (TEE) permits the elimination of the three weeks pre-cardioversion anticoagulation therapy recommended by conventional strategy but,in accordance with non-controlled studies, still requires the prosecution of oral anticoagulation therapy for another 4 weeks due to the cardioversion-related thromboembolic risk. The aim is to verify whether the use of a 2nd TEE 7 days after EC could modify the post-EC therapeutic strategy. METHODS. Once informed consent was given, 101 pts (74 pts with non-valvular AF and 27 pts with flutter and a history of AF >48 hours) underwent a first TEE and, within 24 hours, an EC if there were not present any thrombi, aortic plaques or dense spontaneous echocontrast. Anticoagulation therapy was based on low molecular weight heparin(LMWH-enoxaparine 100 U antiXa/kgx2) for 7 days at which point a 2nd TEE was carried out. In the absence of any new thrombi,dense spontaneous echocontrast and/or low emptying velocity (<40cm/sec) of the left atrial appendage (LAA) the therapy with LMWH was terminated; if this was not the case, anticoagulation therapy, embricated with oral anticoagulation was continued for 4 weeks.Clinical follow-up was performed 1 month,6 months and 1 year post-EC. RESULTS. Sinus rhythm was restored in 71/101 pts after EC which resulted efficacious in 66 pts whilst in 5 restoration in sinus rhythm was spontaneous. After 7 days 55 pts remained in sinus rhythm. The 2nd TEE was refused by 2 pts and carried out in 53 pts. In the follow-up after one month post EC no thromboembolic events were recorded either in the pts at risk who had continued the anticoagulant therapy or in those who had suspended the therapy after 7 days. In the follow-up after 1 year no thromboembolic event was recorded in 87/101 pts with normal LAA velocity, whilst amongst the remaining 14 patients who had shown low LAA velocity, three had a stroke (0% vs 21%: $P<0.001$). In 8/14 low LAA velocity developed only after EC, as recorded by the 2nd TEE. CONCLUSIONS. The TEE 7 days post-EC, which is not to be found in the literature, could well define the timing of the post-EC anticoagulation therapy both for the low risk patients who could take advantage of an early suspension of the anticoagulation based on LMWH, as an alternative to oral anticoagulation, and for those thromboembolic risk patients who should continue oral anticoagulation until the signs of LAA dysfunction disappear.

P1029 Is transoesophageal echocardiography useful before atrial flutter cardioversion?

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The usefulness of TEE before atrial flutter (AFl) electrical cardioversion (EC) is currently controversial. The aim of our study was to assess the incidence of thromboembolism risk factors by TEE before AFl EC.
Methods: 96 AFl without rheumatic heart disease were studied immediately before EC: 18 had ischaemic heart disease, 18 hypertensive cardiopathy, 15 dilated cardiomyopathy, 37 other diseases and 8 idiopathic. Time of the arrhytmia ranged from 2 to 365 days (m:95±128), and could not be determined in 26. 22 patients were chronically anticoagulated. Ejection fraction (EF) and dimensions were quantified by transthoracic study and emptying velocity of left atrial appendage (LAAV) and thrombosis by TEE.
Results: A thrombus in the left atrial appendage was detected in 2 patients: one with AFl duration>1 year and the other with EF 40%. 7 patients had LAAV<25 cm/sec. 26 patients had EF<50%, 21 of these(81%) had LAAV>25 cm/sec and 5(19%)had LAAV<25 cm/sec. Time of the arrhytmia was more than 6 months in 12 patients, 10 of these (83%) had LAAV>25 cm/sec and 2 (17%) had LAAV<25 cm/sec. All 32 patients with EF>50% and arrhytmia duration < 6 months had LAAV >25 cm/sec.
Conclusion: Normal left ventricle function and arrhytmia duration <6 months identify a group of patients at low risk of atrial thrombosis, in whom precardioversion TEE does not appear to be indicated.

P1030 Tissue Doppler imaging and contrast echo for left atrial appendage spontaneous echo contrast quantification by transoesophageal echocardiography

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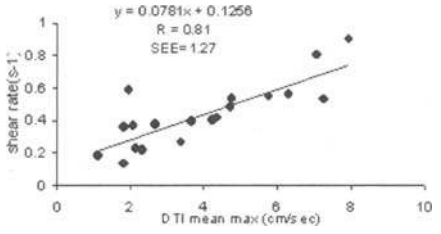
Background: Spontaneous echo contrast (SEC) in the left atrial appendage (LAA) of patients in atrial fibrillation (AF) is associated with thrombus formation and increased risk of thromboembolism. The qualitative operator-dependent appreciation is still the daily practice. Gray scale level quantification was proposed with a complex post-processing. Contrast-agent (CA) provides enhancement of endocardial border detection. Tissue Doppler Imaging (DTI) evaluation with CA has never been evaluated for SEC quantification in patients with AF.
Methods: We analyzed prospectively 20 patients with AF and LAA SEC (mild or severe). A CA (Optison) bolus injection (0.3 ml) was done during transesophageal echocardiography performed always according to the same methodology. The quantitative analysis was done off-line (HDI Lab, Philips). The mean (over 3 beats) maximal velocity of a region of interest (ROI=5x5 mm) was positioned at the LAA mouth. Shear rate was calculated as previously reported as an index of LLA function (2xV/LAA diameter/2).
Results: This DTI index (11.93±7.41cm/sec) was correlated with LAA emptying flow velocities (V) (r=0,72; p<0,001; 0.25±0.11cm/sec) and shear rate (r=0.81, p<0.001; 0.43±0.20 s-1). For the same ROI, normalized (by left ventricular cavity value) gray scale level information without contrast injection (2.37±1.53dB) was correlated with V (r=-0.72, p<0.001) and the shear rate (r=-0.62, p=0.006).



DTI-shear rate correlation.

Conclusions: This first experience of SEC quantification by DTI and contrast-echo is promising. SEC DTI velocities are well correlated with traditional risk factor of LAA thrombus formation. Additional studies will provide the prognosis significance of this new approach in a large number of patients.

P1031 Usefulness of transoesophageal echocardiography in stroke patients with normal transthoracic echoes

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Background: Embolism accounts for approximately 20% of strokes. Stroke patients in sinus rhythm with normal transthoracic echoes (TTE) continue to be referred for transesophageal echo (TEE) to rule out cardiac sources for systemic emboli. The aim of our study was to determine the potential clinical benefit of additional TEE information in stroke patients in sinus rhythm and normal TTE.
Methods: Patients with stroke undergoing TTE and TEE were evaluated. Patients with potential sources of embolism such as: atrial fibrillation, valvular disease including prosthetic valves and left ventricular dysfunction were excluded.
Results: 155 patients with stroke matched our inclusion criteria. The incidence of left atrial enlargement in TTE was 7.7% (n=12) versus TEE 11.6% (n=18) p=n.s., right atrial enlargement in TTE was 2.6% (n=4) versus TEE 3.8% (n=6), p=n.s.; vegetations on aortic/mitral valve in TTE 10,9% (n=17) versus TEE 14.2% (n=22) p=n.s.; patent formamen ovale in TTE 6.4% (n=10) versus TEE 10.3% (n=16); p=n.s., interatrial septal aneurysma TTE 1.3% (n=2) versus TEE 3.2% (n=5); p=n.s. and spontaneous contrast was 10.3% (n=16) in both. TEE however identified severe plaques in the ascending aorta in 15.4% (n=24) of patients. These plaques could not be detected by TTE.
Conclusion: There is no additional significant benefit of TEE in patients with normal TEE in sinus rhythm in identifying sources of embolization. However, TEE identified patients with severe ascending aortic plaques not seen in TTE.

P1032 Transoesophageal echocardiography for prolonged left atrial appendage dysfucntion after electric DC shock for atrial fibrillation

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Background: After electric DC shock (ES) for atrial fibrillation (AF) the sinus rhythm (SR) restoration is not always associated to a mechanical recovery of left atrial appendage (LAA) mechanical function. The aim of this study is to evaluate with transesophageal echocardiography (TEE) the left atrium (LA) and LAA functional behaviour 7 days after ES for AF.
Method: In 63 patients (pts) with non-valvular AF or atrial flutter lasting > 48 hours we performed a pre- cardioversion and a 7-days post-cardioversion TEE study. Left atrial dysfunction was considered when transmitral Doppler A wave velocity (LAv) was < 45 cm/sec (age corrected value) and when LAA emptying velocity (LAAv) was < 25 cm/sec.
Results: At TEE 7-days post-cardioversion we observed atrial and/or LAA dysfunction in 14 out of 63 pts; in 9 pts an isolated LAv reduction, in 3 pts an isolated LAAv reduction, and in 2 pts an associated LAv LAAv reduction. One of the 3 pts with isolated LAAv reduction showed a persistence of a fibrillation-type LAA flow profile, despite a SR restoration and a normal LAv. Serial TEE controls reported a LAA flow profile normalization 3 months after ES.

Cases of LAA or left atrial dysfunction

Patient	1, 2,	3, 4,	5, 6,	7, 8,	9, 10,	11, 12,	13, 14
LAv	38, 40,	40, 50,	45, 34,	71, 32	40, 41,	40, 40,	36, 48
LAAv	45, 40,	44, 25,	36, 43,	18, 38,	25, 20,	40, 44,	35, 15

Conclusion: It is, therefore, evident that in some patients undergoing ES for AF (4.7% of our cases) a persistent LAA isolated dysfunction may occur. Moreover, such dysfunction can last even for a prolonged period of time (3 months). This observation can importantly affect the therapeutic strategy in pts with AF undergoing ES.

P1033 Diagnosis of patent foramen ovale by transthoracic echocardiography using second harmonic imaging: comparison of three contrast agents

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Patent foramen ovale (PFO) diagnosis with atrial right to left shunt is of high importance in patients with an unexplained ischemic cerebral injury.We sought to evaluate whether transthoracic contrast echocardiography with harmonic imaging (TTE) is a diagnostic alternative to transesophageal contrast echocardiography (TEE) and whether the contrast agent composition is of consequence for the detection of patent foramen ovale (PFO) by TTE.
Methods: 121 patients referred for TEE underwent TTE and TEE explorations with one of three different and randomised contrast agents. Contrast agents injected in this study consisted of a mixture of dextrose and air (CA1), polygelatin molecule and air (CA2) and dextrose and blood and air (CA3). The severity of atrial shunting in the left atria was evaluated by two independent observers on TTE and TEE records, as well as the image quality by semiquantitative score. Intensity of contrast agent in the right atria was also assessed by 'off-line' videointensity measurements for CA1, CA2 and CA3.
Results: Total of 23 patients (19%) showed evidence of atrial right to left shunt by TEE. TTE allowed similarly the detection of 23 PFO with a positive and negative predictive values of 87% and 97% respectively. No significant difference was observed between the two techniques. Moreover, concerning the contrast agents comparison, no significant difference was observed between CA1, CA2 and CA3 in term of PFO detection during TTE and TEE. However, quantitative analysis of right atrial contrast showed a higher level of intensity with CA3 compared to CA1 and CA2 during TTE (p<0.05).
Conclusion: In combination with contrast agent injection, TEE and TTE have a comparable yield for the detection of PFO. Although the composition of contrast agent appears not to modify the PFO detection, the contrast quality in the right atria during TTE is the best with a blood, dextrose and air mixture.

P1034 A new screening method for the detection of patent foramen ovale in divers

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Background: Recent studies have shown a relation between patent foramen ovale (PFO) and paradoxical gas emboli in divers. A screening method for the detection of PFO is not available but would be very useful especially in the population of divers. High sensitivity and simple performance are important requirements for such a method. Right-to-left shunt through a PFO theoretically leads to a decrease in arterial oxygen saturation which may be detectable by peripheral oxygen saturation measurements (SO2, %). Therefore, the aim of this study was to assess the value of SO2 measurements to predict a PFO in divers.
Methods: In 71 divers peripheral SO2 was recorded 4 times at baseline as well as immediately after release of Valsalva maneuver in horizontal posture. Divers with a Valsalva induced absolute decrease in SO2 by more than 2% during 1 (criteria A) or at least 2 (criteria B) of the recordings were predicted to have a PFO. After SO2 measurements, contrast transesophageal echocardiography (TEE, reference method) for determination of PFO was performed by operators blinded to the SO2 results.
Results: In 23 of 71 (32%) divers, a PFO was found by TEE. In 19 of these divers PFO was also detected by SO2 measurements using criteria A (sensitivity 83%, specificity 56%). Using criteria B only 15 PFO were correctly detected (sensitivity 65%, specificity 71%)
Conclusion: Peripheral oxygen saturation measurements to detect PFO are easy to apply, harmless and reliable. Of importance for a screening method, the sensitivity for the detection of PFO by SO2 measurements can be improved by lowering the detection criteria, which is particularly useful in the population of divers.

P1035 Right atrial enlargement is an independent predictor for permanent non-valvular atrial fibrillation in the elderly: an echocardiographic study

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Atrial fibrillation (AF) is the most common rhythm disturbance. Its prevalence increases with the age of the population. The relation between left atrial (LA) size and AF is well established in the literature. There is, however, very little data about right atrial (RA) size in non-valvular AF.
Methods: Echocardiographic data including LA area (LA-A) and RA area (RA-A), left ventricular ejection fraction (EF), estimated systolic pulmonary artery pressure (PAP), and the severity of mitral and tricuspid regurgitation (MR and TR), were determined in 286 elderly patients (age >70 years). 126 patients with AF and 160 controls in sinus rhythm. Patients with structural valvular or pericardial disease were excluded.
Results: As expected there was a highly significant correlation between LA-A, PAP, reduced EF ($p<0.0001$ for all comparisons). Patients with AF had more severe MR and TR ($p<0.0001$). RA-A was 16.3+7.3 cm^2 in patients with sinus rhythm as compared to 24.5+5.2 cm^2 in patients with AF ($P<0.0001$). Since RA-A was correlated to the other variables multiple logistic regression analysis was used. Even after controlling for age, gender, LA-A, PAP, EF, MR and TR, right atrial area significantly predicted AF. Each 1cm^2 increase in RA-A was associated with 67% increase in the odds of AF. Backward, stepwise approach from the full model was used with age and gender forced into the equation. In this model the odds ratio for AF increases by 4% with each 1% decrease in EF while each 1cm^2 increase in RA-A is associated with 85% increase in the odds of AF. Comparing patients with only one atrial chamber enlarged (above median) RA-A was much better predictor of AF. 7/49 patients with only LA-A (14%) had AF compared with 35/45 (78%) with RA-A only.
Conclusion: Right atrial size is associated with non-valvular AF in elderly patients.
RA-A is an independent predictor of AF. This association suggests a possible role for RA enlargement in the pathogenesis of AF in the elderly although enlargement of RA secondary to AF is another potential explanation for our findings.

P1036 Haemodynamic progression of aortic valve stenosis in patients with chronic renal failure: a long-term follow-up echocardiographic study

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Background: It has been reported in the last years that elevated serum creatinine is a factor correlated with a more rapid hemodynamic progression of aortic stenosis. It is unclear, however, whether the progression of aortic stenosis is faster only in hemodialysis patients or even a mild-to-moderate increase of serum creatinine could play a role in the acceleration of the progression.
Methods: The adult echocardiographic laboratory database of our department was queried to identify patients with chronic renal failure (CRF) and with at least 2 studies separated by a minimum of 6 months and with an initial peak jet aortic velocity > 2 m/s. Patients with coexisting more than moderate aortic regurgitation were excluded. Inclusion criteria allowed to identify 28 chronic hemodialysis patients and 33 patients with mild-to-moderate CRF (serum creatinine: 2.4±1.1 mg/dl; range: 1.6-6.2). As control group 95 patients with aortic stenosis and normal serum creatinine were rendomly selected from the database. The mean follow-up in all patients was 4±3 years.
Results: Patients with mild-to-moderate CRF were older (71±8 years) of hemodialysis patients (63±10 years) and controls (64±11 years) ($p<0.01$). The first peak aortic jet velocity was 2.7±0.7 m/s in hemodialysis patients, 3.2±0.8 m/s in patients with mild-to-moderate CRF and 3.0±0.7 m/s in controls ($p<0.05$). A pattern of rapid progression, defined as increase of aortic jet velocity > 0.3 m/s per year, was found in 46.4% of hemodialysis patients, in 21.2% of patients with mild-to-moderate CRF and in 20.0% of controls ($p<0.05$). The annual rate of increase in peak jet velocity was 0.39±0.45 m/s per year in hemodialysis patients, 0.16±0.24 m/s per year in patients with mild-to-moderate CRF and 0.17±0.21 m/s per year in the control group ($p<0.001$). The annual rate of reduction in aortic valve area was 0.17±0.18 cm^2 per year in hemodialysis patients, 0.05±0.05 cm^2 per year in patients with mild-to-moderate CRF and 0.06±0.08 cm^2 per year in the controls ($p<0.001$).
Conclusions: Our results confirm that end-stage renal disease and hemodialysis are important predictors of rapid hemodynamic progression of aortic stenosis. On the contrary, patients with mild-to-moderate CRF, despite a higher age, seem to be not significantly different in the progression of the disease as compared with patients with normal serum creatinine.

P1037 ACE I/D polymorphism modifies left ventricular remodelling in pressure overload due to aortic stenosis in men but not in women

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Both gender and cardiac renin angiotensin system (RAS) modify LV remodeling in response to persistent pressure overload. Furthermore, both cardiac and systemic angiotensin levels appear to be related also to the ACE genotype. We tested the hypothesis that the effects of ACE I/D polymorphism on the LV remodeling and function in response to pressure overload due to aortic stenosis (AS) are gender dependent. Accordingly, ACE genotype and levels were prospectively determined in 82 consecutive pts (37 men, 45 women) with pure AS (area <0.8 cm^2). Pts on ACE/angiotensin II receptor inhibitors were excluded from the study. At echo-Doppler study, LV mass and relative wall thickness (RWT = 2 x posterior wall (PW)/LV end-diastolic diameter [EDD]), an index of LV concentric remodeling, were calculated.
Results: *$p<0.05$ vs II using ANOVA, + $p<0.05$ vs Men
DD pts had higher ACE levels than II or ID pts, but respective ACE levels were similar between men and women. In both genders, there were no difference in the AS severity and age (data not shown) and LV mass. In men, the RWT was higher in DD pts vs ID and II pts. In contrast, in women, the RWT was similar in all groups. Furthermore, II women had higher RWT as compared to II men.

ACV genotype		ACE levels (U/L)		RWT (mm/mm)		LV mass (gm)	
Men	Women	Men	Women	Men	Women	Men	Women
II (n=10)	II (n=10)	24±16	23±6	0.29±0.09	0.37±0.07+	224±96	193±53
ID (n=16)	ID (n=20)	33±16	29±13	0.35±0.07	0.36±0.10	193±82	172±81
DD (n=11)	DD (n=15)	44±22*	35±12*	0.45±0.14*	0.44±0.11	232±50	174±40

Conclusion: Thus, despite the similar systemic ACE levels the ACE I/D polymorphism modifies LV remodeling due to aortic stenosis in men but not in women. This suggests that effects of ACE I/D polymorphism on the molecular mechanisms of LV remodeling in pressure-overload hypertrophy are gender dependent.

P1038 Evaluation of isovolumic contraction time by pulsed-wave Doppler tissue imaging. Is it useful in the detection of severe aortic stenosis?

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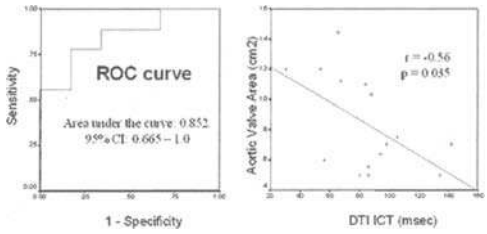
The potential usefulness of pulsed-waved Doppler tissue imaging (DTI) has been mainly evaluated in coronary artery disease and some cardiomyopathies. In patients with aortic stenosis (AS), a delayed left ventricular myocardial contraction has been described. Aim of the study was to evaluate the possible role of DTI in the assessment of AS severity by measuring the isovolumic contraction time (ICT)

We studied 30 patients: 15 with AS (9 severe) and 15 control subjects. Patients were studied by DTI (ICT) and conventional echocardiography, measuring the aortic valve area by the continuity equation. The following was evaluated: 1) Differences in ICT between patients with vs without AS; 2) Relationship between ICT and aortic valve area and gradients in AS patients; 3) Diagnostic value of DTI in the diagnosis of severe AS.

Results: ICT by conventional Doppler was similar in both groups of patients, but DIT ICT was significantly longer in patients with severe AS (98±27 vs. 65±21, p = 0.024). There was a significant correlation between DTI ICT and aortic valve area (r = -0.56; p = 0.035) (see figure). Figure also shows the ROC curve for the diagnosis of severe AS among patients with AS (Area under the curve 0.852; 95% CI: 0.665-1.0). The two best cut-points were a DTI ICT > 73 msec (89% sensitivity, 77% specificity) and > 85 msec (78% sensitivity, 83% specificity).



Relation between ICT and aortic valve.

Thus, ICT as measured by DTI is significantly increased in patients with severe AS, showing a high sensitivity and specificity in the detection of severe AS. These data suggest a new potential clinical application of DTI.

P1039 The unsolved issue of symptoms in severe aortic stenosis: is there a role for the Total Ejection Isovolume Index?

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Background: A Doppler-derived time interval index has been recently proposed: the total ejection isovolume index (TEI index), defined as the sum of isovolumetric contraction and relaxation time divided by ejection time. The value of this index, that combines both systolic and diastolic performance of the left ventricle, has been observed particularly in patients with myocardial infarction and dilated cardiomyopathy. There is however little information about the additional clinical usefulness of TEI index in patients with severe aortic stenosis.

Methods: Ninety-two patients with severe aortic stenosis, defined as continuity equation aortic valve area < 1.0 cm^2, in sinus rhythm underwent echo-Doppler examination (53 males, 39 females; mean age 66±9 years). According to clinical symptoms, patients were classified into two groups: A) Asymptomatic or mildly symptomatic (NYHA I/II): 63 patients; B) More severely symptomatic (NYHA III/IV): 29 patients.

Results: A TEI index >0.45 was found in 14/63 (22.2%) patients in group A and in 23/29 (79.3%) in group B (p<0.001). Aortic valve area was 0.73±0.21 in group A and 0.78±0.21 in group B (p=ns). Maximum Doppler velocity was 4.69±0.75 m/s in group A and 4.66±0.71 m/s in group B (p=ns). There were not significant differences in ejection fraction (60±8% in group A and 57±7% in group B), E/A ratio (0.94±0.77 in group A and 0.88±0.47 in group B), deceleration time (162±71 msec in group A and 163±70 in group B). On the contrary, TEI index was significantly higher in more symptomatic patients (0.40±0.08 in group A, 0.64±0.26 in group B; p<0.001).

Conclusion: In patients with aortic stenosis, the prevalence of a TEI index >0.45 is significantly higher in patients with more severe clinical symptoms. This global performance index seems to be superior to the commonly used systolic and diastolic echocardiographic parameters in identifying patients with worse symptoms. TEI index could help to explain why some patients with severe aortic stenosis have important symptoms while other patients are asymptomatic. This index could then provide a useful tool for the clinical decision making in patients with aortic stenosis.

P1040 The effect of heart rate on the color M-mode Doppler flow propagation velocity and pressure half time in aortic insufficiency

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It has been shown that increased heart rate may improve the hemodynmic condition of patients with aortic regurgitation. Color M-mode Doppler flow propagation velocity (FPV) was introduced as a method to assess the severity of aortic regurgitation. The purpose of this study was to evaluate the effect of heart rate on the color M-mode Doppler flow propagation velocity and pressure half time in aortic insufficiency

Method: Seventeen patients (7 male, 10 female, mean age 52±15 yrs) who had isolated aortic regurgitation of various degrees were included. Color M-mode Doppler was used in FPV while continuous wave Doppler was used in PHT measurements, both in the apical 5-chamber view. Atropin sulfate was titrated in all patients to reach a 20 increase in the heart rate. FPV and PHT of aortic regurgitation were measured before and after the increase of the heart rate.

Results: Increased heart rate resulted in significant decrease in FPV (49.5±14.4 vs 42.1±12.6 cm/sec; p<0.001) and it shortened PHT (476±177 to 376±116 msec; p<0.001).

Conclusion: The FPV and PHT of the aortic regurgitation are rate dependent. The influence of heart rate should be considered in evaluating changes of such parameters in the serial follow-up evaluation of patients with aortic regurgitation.

P1041 Interaliasing distance of the flow convergence surface for determining valvular orifice area in mitral stenosis: initial clinical experience

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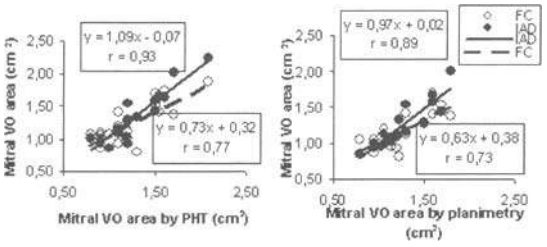
The PISA or flow convergence (FC) method is an alternative to estimate valvular orifice (VO) area in mitral stenosis (MS) when accuracy of pressure half-time (PHT) or planimetry is not warranted. Recently, a new FC method which avoids locating the orifice by measuring the interaliasing distance (IAD) of the FC zone, was validated to quantify mitral regurgitation. Our aim was to evaluate the accuracy of the IAD method to estimate VO area in patients with MS.

Methods: 19 patients with MS were studied with 2D echo. Color Doppler M-Mode images along the centerline of the accelerating flow towards the VO were obtained. The distance between the two first aliasing boundaries proximal to the VO was measured and the FC radius was mathematically derived by the continuity equation (FC radius = IAD*3.41). The conventional FC radius was also measured. VO area was calculated according to the FC method using both IAD and conventional FC radius. Reference standard VO area was obtained by the PHT method and planimetry.

Results: Both mitral VO area calculated from IAD and conventional FC correlated well with VO area by PHT (r=0.93, SEE 0.15 cm^2 and r=0.77, SEE 0.20 cm^2, respectively, n=19)and by planimetry (r=0.89, SEE 0.14 cm^2 and r=0.73, SEE 0.18 cm^2, respectively, n=16)(Graph). There was a trend for a stronger correlation (p=0.07) and a smaller absolute error in favour of IAD (0.18±0.12 vs 0.12±0.10 cm^2, p=0.10).



Conclusion: Good correlation and agreement were observed between IAD-derived mitral VO and two reference methods, and similar to the ones observed with the conventional FC. However,the IAD method does not require spatial localization of the orifice. These data suggest that the IAD method is feasible and accurate to estimate mitral VO in patients with MS.

P1042 TDE reveals insufficient contractile reserve recruitment during exercise-echo in patients with mitral valve prolapse and thick mitral valve

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Mitral valve prolapse (MVP) and thick mitral valve (TMV) have been associated with posterior-inferior wall motion abnormalities. Tissue Doppler echocardiography (TDE) is a promising technique for studying myocardial velocities. The aim of this study was to evaluate the tissue velocities at the basal-inferior wall, during symptom limited exercise echocardiography (EE), in patients (pts) with MVP and TMV.

Methods: Sixteen pts with typical MVP (aged 40±12 years, 20 pts with TMV, all of whom otherwise healthy, and 20 healthy subjects (HS), were studied. All individuals in the aforementioned groups were matched for age and sex. All pts underwent complete baseline echocardiographic study and EE. Peak systolic velocities (S) at the basal-inferior wall were measured by TDE at rest and immediately after the peak of the exercise. Mitral regurgitation (MR) was assessed by color Doppler. Statistical analysis was made with t-test, x2 and multivariate analysis which was performed with Cox regression.

Results: Baseline and peak exercise heart rate and blood pressure did not differ among MVP pts, TMV pts and HS. No wall motion abnormalities (either at rest or at the peak of the exercise) or significant changes in MR were observed in our study population. MVP pts developed in an earlier stage fatigue and dyspnea during the exercise test as compared with the other groups of pts. At rest S was greater in MVP pts (S=12.3±3cm/sec) compared with both, TMV pts (S=10.5±2cm/sec, $p<0.01$) and HS (S=9.5±1cm/sec, $p<0.0004$). During exercise the increase in S was significantly lower for MVP pts (S=17.3±5cm/sec, p=0.0008) and TMV pts (S=15.5±2.1cm/sec, p=0.0007) compared to HS (S=19.8±4cm/sec, p=0.0001).

Conclusions: i) No evidence of wall motion abnormalities was found with 2D echocardiography in MVP and TMV pts. ii) Systolic velocities at the basal-inferior wall in the aforementioned pts did not increase in response to exercise, suggesting insufficient contractile reserve recruitment. iii) The above velocities were higher in the resting state, probably due to the augmented adrenergic tone.

P1043 One-year echocardiographic follow-up of left-sided valvular disease in carcinoid syndrome

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Background: Right-sided valvular disease is well known in carcinoid syndrome but little is known about the left-sided valvular disease. The aim of our study was to assess the incidence of both right and left-sided valvular diseases and to determine the role of patent foramen ovale (PFO) with this left-sided valvular disease.

Methods: Forty-six consecutive trans-thoracic echocardiographies (TTE) have been performed in 23 pts (mean age 60 ± 8 years, 52% women) presenting with carcinoid syndrome, at control and at one-year follow-up. The echocardiographic following parameters were assessed: 1) right-sided valvular disease, 2) left-sided valvular disease, 3) right to left shunting through a patent foramen ovale (PFO +) using contrast echocardiography at rest and after cough test or Vasalva maneuver.

Results: At control, TTE revealed 6 pts (26%) with right-sided valvular carcinoid disease (RVCD), 3 pts (13%) with left-sided valvular carcinoid disease (LVCD) and 8 PFO + (35%). At one year, the incidence of RVCD, LVCD and PFO + was 30% (7 pts), 23% (5 pts) and 39% (9 pts) respectively. All patients with RVCD and PFO + exhibited progression or new appearance of left-sided valvular disease.

Conclusion: According to follow-up, our data suggest that the incidence of left-sided valvular injury is higher than previous studies in carcinoid syndrome. PFO + resulting in right to left shunting seems to be a major factor of left-sided valvular injury and should be systematically researched in carcinoid syndrome.

P1044 Aortic valve calcification in hypertensive patients: prevalence, risk factors and association with transvalvular flow velocity

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Background: The important role of the "nonobstructive" aortic valve calcification (AVC) in cardiovascular morbidity and mortality has recently been emphasized. Data regarding the factors determining the extent of AVC and its interrelationship with flow velocity across the aortic valve are scarce and discordant. The present work had two goals: 1) To analyze the prevalence and the factors determining the extent of AVC in hypertensive patients; 2) To investigate a possible association between the extent of AVC and flow velocity across the aortic valve in patients without established aortic stenosis.

Methods: It was a prospective comparative crossectional study performed in a cardiology department in a general hospital. The study sample consisted of 263 consecutive patients (139 men and 124 women, aged 52-79 years, mean 65±6), who underwent echo-Doppler. A calcified deposit of <2 mm in its highest thickness was defined as minimal, a deposit ranging from 2 to 5 mm as mild and a calcified deposit of more or equal than 5 mm, as significant. Advanced AVC was defined as follows: a) Presence of at least one significant calcified deposit or b) Presence of 2 or more mild calcified deposits. There were 31(12%) patients in the advanced AVC group and 122 (46%) patients without any calcified deposits (the No AVC group). The remaining 110 (42%) patients who did not meet criteria of the advanced AVC comprised the Trivial AVC group.

Results: The upper quartile of peak flow velocity across the aortic valve (>130 mm/sec in our population) was defined as augmented flow velocity. Peak flow velocity across the aortic valve was significantly higher in patients with advanced versus trivial AVC and no AVC groups: 135±45, 116±23 and 113±23 mm/sec, respectively; p=0.0002. Prevalence of augmented transvalvular aortic flow was significantly higher (p=0.01) among patients with advanced AVC (41.9%) versus trivial (20.9%) and no AVC (29.5%). Multivariate analyses identified age as the only independent variable associated with advanced AVC [OR 1.6 (CI 1.2-2.3), 5 years increment] and any AVC [OR 1.5 (CI 1.2-1.9)]. Advanced AVC and female gender were identified as independent variables for augmented transvalvular aortic flow with OR 2.9 (CI 1.3-6.4) and 2.5 (CI 1.4-4.6), respectively.

Conclusions: Prevalence of AVC among hypertensive patients is high and clearly age-related. Advanced (but not trivial) AVC is associated with augmented aortic transvalvular peak flow velocity despite unrestricted opening of the valve leaflets.

P1045 Influence of postoperative anemia on valve gradient measurement by Doppler echocardiography

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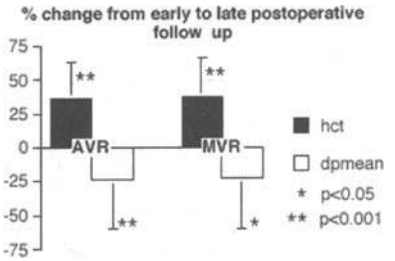
Background: The accuracy of early postoperative Doppler echocardiographic gradient measurements after valve replacement may be affected by postoperative anemia.

Purpose: To assess the influence of the postoperative recovery of hematocrit (hct) and hemoglobin values on the Doppler measurements of valve gradients.

Methods: Transthoracic Doppler echocardiography was used to assess postoperative valve function.

Results: In 38 patients maximal instantaneous (dpmax) and mean (dpmean) pressure gradient was assessed 10+5 days and 268+318 days after aortic valve replacement (AVR). In 12 patients dpmean and pressure half time (p/2-time) was assessed 10+5 and 306+311 days after mitral valve replacement (MVR). In AVR dpmax decreased from 26+12 to 20+9 mmHg ($p<0.005$) and dpmean from 14+8 to 11+6 mmHg ($p<0.005$). In MVR p/2-time remained unchanged (76+18 vs 76+14 ms) but dpmean decreased significantly (5+1 vs 4+2 mmHg, $p<0.05$). This was paralleled by an increase in hct (28+4% to 38+6%, $p<0.0001$) and hemoglobin (9.2+11.4 g/dl to 12.3+2.0 g/dl, $p<0.0001$) in AVR aswell as in MVR (28+4% to 37+5%; $p<0.0001$ and 8.9+1.4 to 12.2+1.8 g/dl; $p<0.0001$). See figure.



Conclusions: Early postoperative Doppler echocardiographic routine gradient measurements after valve replacement should not be used as baseline characterization for future follow up because they may provide misleading results due to the hyperdynamic state induced by postoperative anemia.

P1046 Cardiac involvement in pulmonary sarcoidosis. An echocardiographic evaluation study

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Background: Sarcoidosis is a multisystem disorder of unknown aetiology characterised by infiltration of several organ system by caseating granulomes. The aim of this study was to identify the presence and patterns of cardiac involvement in patients (pts) with pulmonary sarcoidosis.
Methods: We studied 53 consecutive pts with pulmonary sarcoidosis (45 women, age 49 ±13 years), without cardiac disease, followed in an ambulatory specialised clinic. Clinical data: NYHA functional class; sarcoidosis stage (0 to 3); disease duration, RFT and corticotherapy. Echocardiographic study included the analysis of cavities dimensions, left ventricle (LV) walls hyperechogenicity, systolic LV function and Doppler measurements of mitral and tricuspid flows (E/A ratio, desacceleration time, A wave duration); pulmonary venous flow (s, d and a waves, a wave duration), systolic tricuspid flow (in patients with tricuspid regurgitation) and pulmonary valve flow (acceleration and ejection times).
Results: Half of the pts had at least one echocardiographic abnormality. In 21 (33%) there was hyperechogenicity of the ventricular septum, suggestive of possible myocardial infiltration, in 20 (36%) there was right ventricular enlargement, in 20 (36%) pulmonary valve flow had criteria for pulmonary hypertension. Left ventricle diastolic dysfunction (LVDD) pattern found in 14 subjects, 12 with impaired relaxation and 2 with restrictive physiology. In twelve pts, the tricuspid flow desaceleration was above 210 ms.
Association with clinical data: (1) Septum hyperechogenicity: was less frequent in pts who had been previously treated with corticosteroids (35% vs. 64%; $p<0,05$); was associated with lesser tricuspid valve inflow velocity ($r= -0.55$ $p<0.01$) however was associated with the pulmonary artery systolic pressure ($r= 0.55$ $p<0.05$); (2) Longer the disease duration higher the incidence of LVDD ($p<0.01$). Pts with disease duration lesser than 5 years did not have LVDD.
Conclusions: Echocardiographic abnormalities are frequent in subjects with pulmonary sarcoidosis and there is a possible relationship between the valvular Döppler flow patterns, pts clinics and corticotherapy.

P1047 Impact of Transoesophageal Echocardiography (TEE) in the diagnosis and outcome of patients with infected pacemaker and defibrillator leads

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Background: Infection is one of the most important indications for pacemaker and ICD lead extraction as infection rate of these devices ranges from 4-7%. Ten years ago the morbidity and mortality from infection of these devices without explantation was around 60%. This emphasizes the importance of rapid and accurate diagnosis of infection leading to the removal of the entire system as soon as possible The clinical manifestation of infection are multiple: fever, local inflammation, erosion, endocarditis and vegetation. With the use of echocardiography especially Transesophageal Echocardiography (TEE), clinicians can make accurate and fast diagnosis of infection thereby helping in the diagnosis and management of this devastating problem.
Purpose: Assessment of the impact of TEE on the planning, performance and outcome of pacemaker and defibrillator lead extraction.
Method: Prospective data analysis was done on all patients treated at Hahnemann University Hospital from Jan.1991- Nov.2001 for lead extraction. Only patients who had TEE done before or after lead extraction were included.
Results: 100 patients with 250 leads were dignosed with device related infection with the help of serial blood cultures and TEE. TEE confirmed the device infection in 2 patients with negative blood cultures. During pre-operative TEE, vegetation was found in 22 patients. Vegetation ranged in size from 0.2 to 3 cm in largest dimension. Infection was caused by Staphylococcus in 82% patients, Enterobacter 5%, Pseudomonas 5%, Streptococcus 5% and 1% each by Candida, Citrobacter, Cornybacterium, and Propionibacterium. Complete device removal was achieved in 95% patients. Postoperative TEE was performed in all patients with vegetation. Reimplantation of a new device was performed in 84% patients after negative blood culture and negative TEE. No TEE related complications were noted.
Conclusion: We conclude that TEE is the diagnostic tool of choice in the patients with clinical suspicion of lead infection. TEE monitoring during lead extraction provides real time information enabling the operator to better plan the procedure and rapidly diagnose complications. TEE also provides guidelines about the time frame of reimplantation of new device.

P1048 Biventricular pacemaker/ICD-implantation in the operating room: guidance of coronary sinus intubation by transoesophageal echocardiography

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Biventricular pacing has been introduced to improve quality of life and cardiopulmonary performance in patients with advanced congestive heart failure. Location and implantation of the additional left ventricular electrode via the coronary sinus (CS) in cardiac veins is significantly prolonging the duration of surgery as the crucial point of the procedure. In the setting of anteroposterior fluoroscopy technique in the operating room additional transesophageal echocardiography (TEE) was used to guide proper lead placement and verification of lead location and for immediate hemodynamic monitoring.
Patients and methods: 25 patients with severe congestive heart failure (NYHA class 3.2 mean) were enclosed in the study. Underlying heart disease was coronary heart disease (n=9) and dilated cardiomyopathy (n=16). The patients received a biventricular pacemaker or ICD (Medtronic InSync, Guidant Contak CD/TR). During the procedure additional intraoperative echocardiography was applied. Guidance of CS-intubation, final electrode position, mean QRS-width, NYHA-class, exercise capacity and ejection fraction, were analysed during follow up. Results: CS intubation could be guided in all cases by TEE. The mean ejection fraction, NYHA-class increased significantly (24%±8.2% vs 34,2±8.7% and 3.1±0.16 vs 2.2±0.54), QRS-width decreased significantly (168± 22ms vs 135±15 ms) ($p<0.05$).
Conclusions: 1. In the absence of intraoperative biplane fluoroscopy technique transesophageal echocardiography improves coronary sinus intubation and time for lead placement. 2. Biventricular stimulation established significant benefit for the patient in this implantation setting.

P1049 The association between aortic atheroma and ischaemic cardiomyopathy

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Objective: The association between the pathogenesis of aortic atheroma (AA) and ischemic cardiomyopathy (ICM) has not been established. We studied the correlation between the presence and degree of AA with the presence or absence of coronary artery disease (CAD).
Method: We studied 81 patients (pts) with a diagnosis of cardiomyopathy who had undergone both transesophageal echocardiography (TEE) and cardiac catheterization (CC) between 1996 and 2002. A luminal diameter narrowing of > 70% in one or more epicardial arteries was considered significant for CAD. Pts were classified into a non-ICM group (normal coronary arteries) and an ICM group (presence of one or more epicardial CAD). We documented the presence, location and degree of significant AA (plaque grade > 3). Clinical, TEE and CC parameters were analyzed. Statistical analysis was performed by ANOVA t-test and Spearman's correlation test.
Results: 29 (60.4%) pts in the ICM group had significant atherosclerosis of the ascending aorta and aortic arch compared to 2 (6.1%) pts in the non-ICM group ($p<0.0001$). Multivariate analysis showed hypertension (HT), smoking and diabetes mellitus (DM) to be more common in the ICM group than in the non-ICM group (Table 1). A close association was observed between the presence of CAD and the severity of the plaque in the ascending aorta ($p< 0.0001$), aortic arch ($p< 0.0001$), and descending aorta ($p< 0.0001$). Multivariate analysis of other clinical variables such as age, sex, history of alcohol abuse, stroke, history of viral myocarditis, hyperlipidemia, medications and other TEE and CC variables were not significant.

Risk Factors	ICM (n=48)	N-ICM (n=33)	p-value	RR (95% CI)
Smoking	42 (87.5%)	4 (12.9%)	0.0001	24.5 (7-85.2)
HT	41 (85.4%)	9 (31%)	0.0001	13.7 (4.5-41.9)
DM	19 (39.6%)	4 (12.9%)	0.009	4.6 (1.4-15.2)
Significant AA	29 (60.4%)	2 (6.1%)	0.0001	23.7 (5.1-110.6)

Clinical and echocardiographic predictors of ischemic cardiomyopathy (RR=relative risk, CI=confidence interval)

Conclusion: As expected, traditional risk factors such as smoking, HT, and DM are associated with ICM. In addition, the presence and severity of AA is strongly associated with ICM. Conversely, the absence of significant AA has a high negative predictive value for excluding ICM (93.9%).

P1050 Fibrinolysis and thrombosis of mechanical prosthetic valve: risk stratification by TEE

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Fribrinolysis treatment in prosthetic valve thrombosis appears to be an attractive alternative to surgery but is still controversial because of the well-known embolic risk. The objective of this study was to assess the impact of TEE upon the risk stratification.
Methods: We analyzed 49 patients with a prosthetic valve thrombosis confirmed by TEE and subsequently treated by fibrinolysis. The involved prosthetic valves were mitral for 37, aortic for 11 and tricuspid for 1. We observed 11 non obstructed thrombosis (NOT) and 37 obstructed (OT). Clinical events and fibrinolytic treatment efficacy were studied related to the criteria of valve obstruction and to the thrombus size < 10 mm (n = 33) or superior or equal to 10 mm (n = 16).
Results: Complete recovery of the normal prosthetic motion was achieved by the fibrinolysis regimen in 34 patients (69.4%). In term of complications, we observed 2 early cerebral haemorrhages (4.1%) one in the NOT group and one in the OT group, 6 peripheral embolisms (12.2%) (one in the NOT group). No significant statistical association was found between thrombus size and embolic event rate. However, the risk of treatment failure and/or complications (embolism) was related to the thrombus size (full success when thrombus size < 10 mm: 82% versus 35% when thrombus size is superior or equal to 10 mm, $p < 0.05$). Conclusion: TEE is of major interest in the management of prosthetic valve thrombosis. As far as FT is considered it will be safer and more effective when thrombus formation is small.

P1051 Co-relation of flow sample curves in Coronary Sinus with the Pathophysiology coronary circulation analyzed by transoesophageal echocardiography

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Background: Thansoesophageal echocardiography (TEE) has proved to be a useful method to evaluate coronary flow velocity analysis in coronary sinus (CS) using Doppler measurement during continuous infusion of adenosine.
Objective: Our study had the propose to evaluate systolic velocity (SV), diastolic velocity (DV) and flow sample curves morphology within CS in healthy volunteers and Patients with obstructive coronary arteries lesions before and after Coronary Artery Bypass Graftings (CABG) with intravenous adenosine infusion.
Methods: Through TEE with adenosine infusion in a dose of (140ug/Kg/min for 4 min) adequate flow velocity and morphology curves were evaluated within CS in 10 healthy volunteers (mean age 37 ± 8 years; 5 women) and 23 patients (mean age of 68 ± 14 years; 17 men) with multiarterial obstructive lesions (>70% luminal diameter narrowing) before and 52 ± 16 days after CABG.
Results: Flow velocities in healthy volunteers and patients before and after CABG are shown in table 01. CFR in the control group was (3,5 ± 0,33 4°min) and in patients pre and post bypass surgery (1,7 ± 0,27 4°min, 3,1 ± 14 4°min) respectively. Differences pre and post procedures were considered significant when P<0,05.

Table 1: Systolic Flow Velocity in CS

Condition	Normal SV	pre-CABG SV	post-CABG SV
basal	39±8 cm/s	32±6 cm/s	39±5 cm/s
Aden 1 min.	68±18 cm/s	38±6 cm/s	50±8 cm/s
Aden 2 min.	88±20 cm/s	41±9 cm/s	58±13 cm/s
Aden 3 min.	106±22 cm/s	53±7 cm/s	73±15 cm/s
Aden 4 min.	111±19 cm/s	58±10 cm/s	80±17 cm/s

Abbreviations:CS=coronary sinus; Aden=adenosine; min=Minute; SV=systolic velocity; CABG= coronary arteries bypass graftings.

Conclusion: Flow velocities (SV and DV) and CFR in CS increased during adenosine infusion in healthy volunteers and patients before and after procedures, but in patients without reaching the level of the normal flow velocities.

MAGNETIC RESONANCE IMAGING: WHAT'S NEW?

P1052 Assessment of stress induced reduction of subendocardial bloodflow in patients with coronary artery disease with magnetic resonance imaging

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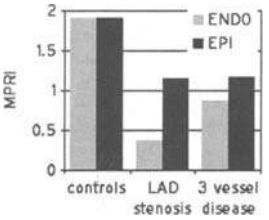
Subendocardial perfusion is highly sensitive for the detection of myocardial ischemia, however, current methods, such as SPECT and PET lack sufficient spatial resolution to discriminate between different layer. MR perfusion measurements offer sufficient spatial resolution. Our aim was to assess, whether separate analysis of subendo- (ENDO) and subepicardial (EPI) perfusion increases diagnostic accuracy for the detection of significant coronary artery disease (CAD).
Methods: 47 patients (pts) (30 male, age 62±7 yrs) with previous invasive angiography were included. 17 pts had single vessel CAD, 20 three-vessel disease, and 10 no significant CAD. Pts were examined with a 1.5 T MR scanner (Philips ACS NT) at rest and during adenosine stimulation (140µg/kg bw) and the first pass of a contrast agent (Gd-DTPA 0.025mmol/kg bw) injected as a peripheral bolus was visualized in 5 short axis views (TFEPI, TE/TR/flip 3.3/12/30, spatial resolution 1.7x2.2 mm). The myocardium was divided into 6 endo- and epicardial segments per slice (60 segments total) and the max. upslope of the myocardial signal intensity time curves was determined. Myocardial perfusion reserve index (MPRI) was calculated as the upslope at stress divided by the upslope at rest.
Results: A close correlation between ENDO and EPI was found (r^2=0.85) with a 35% higher ENDO perfusion in comparison to EPI. At rest, MPRI was similar for ENDO and EPI. At stress, ENDO perfusion was reduced to a higher extent, than EPI. Diagnostic accuracy improved from 89% (transmural) to 94% (ENDO).



Conclusions: MR perfusion measurements allow the differentiation of subendo- and subepicardial blood flow. Subendocardial perfusion is more sensitive to ischemia, than subepicardial perfusion resulting in an improvement of diagnostic accuracy.

P1053 Rapid evaluation of myocardial viability by contrast-enhanced MRI using a three-dimensional inversion-recovery (IR) sequence

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Delayed contrast-enhanced magnetic resonance imaging (DCE-MRI) allows assessment of myocardial viability in patient with ischemic heart disease. The current approach requires multiple breath-holds to generate a set of images covering the left ventricle which is time-consuming and may introduce misregistration of slices. We evaluated a novel approach using a 3D sequence which allows complete data acquisition within one breath-hold.
Methods: 10 patients with chronic coronary artery disease (62±12 years, 3 females) underwent DCE-MRI on a 1.5T MR scanner (Sonata, Siemens, Erlangen, Germany) for viability assessment 15 minutes after 0.2 mmol/kg Gadolinium-DTPA. For the standard approach we used a 2D segmented IR gradient-echo sequence (25 segments, TR/TE 9.6/4.4, FA 25°, TI 250-300 ms, matrix 208x256, resolution 1.3x1.6x5mm) with data acquisition every other heartbeat. For the 3D approach we used a segmented IR gradient-echo sequence (77 segments, TR/TE 2.8/1.1, FA 25°, TI 200-230 ms, matrix 256x208x12, resolution 1.4x1.4mm, slice thickness 8.3mm reconstructed to 5mm) with data acquisition every heart beat. Double oblique short-axis views covering the left ventricle were acquired with identical orientation using both sequences. In matched images total myocardial areas and DCE areas for both techniques were assessed and the signal to noise ratio (SNR) for DCE myocardium as well as contrast to noise ratios (CNR) for DCE vs. non-DCE myocardium and blood was calculated. The accuracy of the 3D sequence to detect the presence of DCE compared to the 2D sequence was evaluated in 8 sectors per slice in each patient. Observer agreement for the presence and the transmurality of DCE was evaluated in a randomized, blinded fashion.
Results: Imaging was successful in all patients. Myocardial areas and DCE areas were not different between the 2D and 3D sequence (p=ns). The accuracy of the 3D sequence to detect the presence of DCE was 92%. SNR and CNR were 3 to 4-fold larger for the 3D sequence compared to the 2D sequence. Agreement between two observers was 95% for the presence of DCE (Kappa=0.90) and 88% for the transmurality of DCE (Kappa=0.77).
Conclusions: Detection of DCE using the 3D sequence is feasible in one single breath-hold and accurate compared to the standard 2D sequence. The improved SNR and CNR facilitate recognition of the DCE area. This fast sequence should be used for rapid screening for the presence of DCE. Acquisition of selected images using the 2D sequence can be added for accurate quantification of the transmural extent of DCE.

P1054 Assessment of perioperative myocardial infarction associated to coronary artery bypass surgery using contrast-enhanced magnetic resonance imaging

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Background: It is unknown whether routine, successful coronary artery bypass surgery (CABG) is associated with perioperative myonecrosis. Contrast-enhanced MRI (ceMRI) is able to visualize both transmural and subendocardial myocardial infarction (MI). Hereby, MI is represented by hyperenhancement (HE).
Methods: 48 patients (pts) underwent cine and ceMRI before and after CABG on a 1,5 T scanner (SONATA, Siemens). The pattern of hyperenhancement (HE) and regional myocardial function was compared using a 72-segment model. The amount of new hyperenhancement (HE) after CABG and ejection fraction (EF) was quantified by planimetry. ECGs were analyzed as to presence of Q-waves using the Minnesota-Code.
Results: Before CABG, 18 pts (38%) had electrocardiographic Q-waves but 38 (79%) had evidence of prior MI (HE present). After CABG, only 6 pts (10%) had new Q-waves but 20 (48%) had new areas of HE. The median mass of perioperative myonecrosis based on the volume of new HE was 5.4 gm (0.3-48.9) or 2.1% (0.1-33.0%) of left ventricular mass. EF increased 7.1+9.5 points and the level of improvement was not different between pts with and without new HE (P=0.66). Regional contractility, however, showed significantly more improvement after CABG in patients without new HE ($p<0.0001$).
Conclusions: Perioperative myocardial damage is common following routine, successful CABG. The rate of new MI is significantly underestimated by electrocardiographic criteria but the volume of necrosis is small and appears to have minimal impact on the level of contractile improvement following CABG. Improvement of regional function, however, is impaired in patients with new MI.

P1055 The sensitivity of heavily T2-weighted MRI to detect acute myocardial infarction – Relation to "delayed enhancement"

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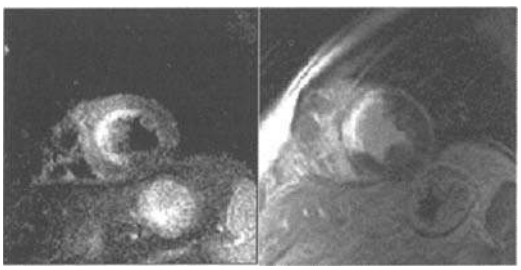
Background: Heavily T2-weighted magnetic resonance imaging (MRI) is suitable for the detection of the tissue edema. Newer techniques such as triple-inversion-recovery-based SE sequences show a reproducibly high image quality with an excellent contrast-to-noise in detecting tissue edema. Especially the sensitivity of this technique in acute myocardial infarction, however, is unknown.
Patients and Methods: We have studied 51 patients (age 59±13y.) 3±1 days after acute myocardial infarction, as defined by clinical means, typical ECG patterns, elevated troponine T, and invasively confirmed related coronary occlusion or stenosis. In a 1.5 T MRI scanner using a body coil and a short-TI-inversion-recovery sequence (STIR, TE 64ms, TR 2 RR intervals, TI 140ms, acquisition time 16 to 20 sec) in 3 short axis views. Results were compared to contrast-enhanced inversion-prepared gradient-echo images ("delayed enhancement", TI 220 to 250msec) in the same slice position. A blinded analysis was performed.
Results: Image quality was adequate to excellent for the diagnosis in all cases. In all patients, the infarct-related region revealed a bright signal intensity (sensitivity 100%). Fig. 1 shows infarct-related edema (left panel) and delayed enhancement (right panel) of an anteroseptal infarction. The edematous area tended to slightly extend that of the area of "delayed enhancement". An intraluminal high-intensity signal area was also observed (see fig. 1).



Conclusion: Heavily T2-weighted MRI allows the confirmation of suspected acute myocardial infarction with an excellent sensitivity. Thus, in a clinical setting, contrast-enhanced MRI may only be necessary for more chronic infarctions. However, an overestimation of the infarct size may occur.

P1056 Plaque-targeted MRI contrast media; introducing a novel SPIO contrast media for magnetic resonance imaging of macrophage infiltration in vulnerable plaque

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SPIO (super paramagnetic iron oxide) is a MRI blood pool contrast media in the form of nano-particles consisting of a central core of iron oxide traditionally coated by colloidal polysaccharide mainly dextran. We have shown that dextran-coated SPIO including the commercially available SPIO (Feridex) is taken up by macrophages in atherosclerotic plaques of Apo E K/O mice and Watanabe rabbits. However, their uptake was followed by a significant rise in intracellular oxidative enzyme activity mainly due to respiratory burst associated with the digestion of dextran in macrophages. Also we needed to increase macrophage uptake in lipid rich plaques. Here we report a novel liposomal SPIO. We hypothesize that lipid-coated SPIO particles enter macrophages through a different pathway allowing more uptake with less oxidative stress.
Methods: Mouse peritoneal macrophages were isolated in the culture medium and incubated with different SPIOs for 4 hrs and then washed. After 24 hrs, production of NO was measured in supernatant by Greiss reagent. In a second series of experiments fluorescent-labeled SPIO (FL-SPIO) was added to macrophages in the presence of two inhibitors of mannose receptor: dextran and mannan. Intracellular retention of FL-SPIO was measured after 2 hrs in 4 groups of macrophages with SPIO, SPIO and dextran, SPIO and mannan and no SPIO as control.
Results: See Figure 1 ($p<0.05$). Also FL-SPIO studies showed that mannan a known inhibitor of mannose receptor significantly inhibited macrophage uptake of dextran coated SPIO but not lipid coated SPIO.

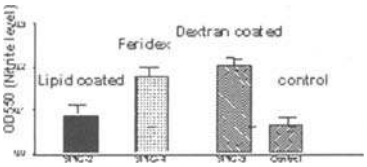

Fig. 1: NO production by dextran coated vs. lipid coated SPIO particles in macrophages 24 h.

Conclusion: Liposomal SPIO is a promising candidate for contrast-enhanced MR imaging of macrophage infiltration in vulnerable plaque. Receptor-targeted liposomal SPIO may further improve plaque-targeted MR imaging.

P1057 Prognostic value of a residual false lumen in aortic dissection submitted to surgery. A magnetic resonance prospective study

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Patients (pts) with aortic dissection submitted to surgery remain at risk of long-term complications. The aim of this study was to assess the prognostic influence of the presence and permeability of a residual false lumen, in pts operated for aortic dissection with involvement of ascending aorta.

Methods: We studied 43 pts, 23 men, with a mean age 53.8±1.7, operated for Stanford type A aortic dissection (ascending aorta replacement in 22 pts, with valve resuspention in 7, with aortic valve prosthesis in 9 and Bentall procedure in 5). All pts were submitted to a magnetic resonance study (MRI) at two months after surgery and, afterwards, annually, for three years. MRI study included: fast spin echo, in axial, coronal and oblique sagital planes; fast gradient-echo in axial plane; cine MR in selected planes, for flow evaluation and aortic valve function. For analysis, aorta was classified in four segments: ascending (proximal to the aortic graft), arch, descending thoracic and abdominal. Endpoints: aneurysm (thoracic segments > 49 mm and abdominal > 39 mm), pseudoaneurysm or aortic valve regurgitation development.

Results: Total follow-up time was 39.1±2.7 months. At initial evaluation, no pt had aneurysm and none had more than mild aortic valve regurgitation. During follow-up, aneurysms were detected in 31/167 segments of 19 pts (41.9%) and moderate or severe aortic regurgitation developed in 12 (42.9%). A residual false lumen was present in 73 segments of 24 pts (in 19 involved all distal aorta), which remained present during follow-up. There was persistent patency of false lumen in 63 segments (86.3%), thrombosis in 2 (2.7%) and variable patency in 6 (8.2%). A false lumen in arch was associated with a 6.6 relative risk (RR) for aneurysm in the same segment (95% c.i.,1.8-23.8, p=0.001), while in descending thoracic with a 2.3 RR (95% c.i.,0.9-6.8, p=0.01) and in abdominal with a 2.3 RR (95%c.i.,0.7-8.6, p=0.01). Patency patterns weren't associated to increased risk of aneurysm. False lumen presence and patency didn't have influence on aortic regurgitation.

Conclusions: In this prospective MRI study, patients operated for aortic dissection with ascending segment involvement had high incidence of long-term complications. The presence of a residual aortic false lumen was associated with increased risk of aneurysm development.

P1058 Simultaneous assessment of wall motion and perfusion during high-dose dobutamine-atropine stress MRI improves diagnosis of ischaemia

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Introduction: With MR, both the assessment of wall motion during high dose dobutamine stress (DSMR), and of myocardial perfusion during adenosine stress are highly accurate. Since high-dose dobutamine has been shown to fully exhaust myocardial resistance, like the direct coronary vasodilator adenosine, we investigated whether a simultaneous assessment of wall motion and myocardial perfusion reserve during the same DSMR examination improves diagnosis of ischemia.

Methods: 80 consecutive pts (59±8 yrs; prior myocardial infarction 50%; prior percutaneous or surgical revascularization in 83% and 20%) underwent DSMR (1.5 T Philips), prior to clinically indicated invasive coronary angiography. DSMR images were acquired at rest and during a standardized high-dose dobutamine-atropine protocol in 3 short-axis, a 4- and a 2-chamber view (single-slice segmented GRE; TR/TE/flip 5.6/1.9/25; spatial res<1.5x2.5x8 mm; temporal res<30 ms). Regional wall motion was assessed by consensus between 2 blinded observers using a multiple screen format (MASS 4.2, Medis), a 16 segment model and a four-point scoring system. DSMR was defined as positive for ischemia in the presence of a new or worsening wall motion abnormality in >=1 segment. During the same stress test (only at rest and 20 μg.kg-1.min-1), myocardial perfusion was assessed during the first pass of a gadolinium-DTPA bolus from 60 dynamic images acquired every heartbeat (3 identical short axis views; single shot TFE-EPI hybrid sequence with saturation prepulse; pp-delay 200 ms; TR/TE/flip 3.6/12/30; spatial res<2.4x2.4x8 mm). Myocardial perfusion reserve was calculated from the alterations of the upslope of the signal intensity time-curve (MASS) and segments were classified as ischemic or normal according to a previously determined threshold.

Results: Significant CAD (>=50% diameter stenoses by QCA) was found in 57 pts (71%). Wall motion analysis was non-diagnostic in 8 pts (10%, target heart rate not reached) and perfusion measurements in 26 pts (33%, poor image quality). Sensitivity and specificity of wall motion analysis for detection of significant CAD were 86% and 81%, as compared with 92% and 53% for perfusion analysis, and 87% and 78% for a combined analysis, with only 4% non diagnostic examinations.

Conclusions: A simultaneous assessment of wall motion and myocardial perfusion reserve during DSMR is safe and feasible in pts with known CAD. Compared with wall motion analysis alone, diagnostic yield is improved. However, the diagnostic accuracy of perfusion measurements alone is relatively low with the stress scheme applied.

P1059 Measurement of vasodilator reserve in coronary grafts using magnetic resonance tomography

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Introduction: Atherosclerosis of coronary grafts is a common clinical problem. MR vasodilator reserve measurement using adenosine is used for noninvasive hemodynamic assessment of coronary grafts, whereas most noninvasive imaging modalities can only provide information about their patency. The aim of the study was to evaluate the potential of this method to discriminate stenosed from patent coronary grafts.

Methods: MR measurements were performed on a 1.5 T system (Siemens, Vision) using a body array coil in 36 patients with a total of 51 coronary grafts (14/51 IMA-LAD, 16/51 vein grafts LAD, 21 vein grafts RCA/CX). MR provides adenosine vasodilator reserves for blood velocity and flow measurements using a breathhold phase change technique (TR/TE: 24/5 ms, VENC 75 cm/sec). During the cardiac cycle 5-6 image pairs were acquired and mean flow and mean velocity were measured integrating the data over the cardiac cycle.

Coronary grafts were imaged by conventional invasive angiography within 48 hours of MR measurement. Graft stenosis was measured quantitatively by AWOS System (Siemens).

MRI HASTE imaging was used to visualize the course of the grafts. Perpendicular to the course the first MR flow measurement in breath-hold technique was planned. Afterwards adenosine infusion was started and a second flow measurement was performed.

Target parameters were the vasodilator reserves for mean flow, mean velocity and peak velocity.

Results: In 3 patients and 3 grafts the imaging quality was insufficient. The results of 33 patients and 48 grafts were included in the final results. Angiographically no atherosclerosis was present in 36 grafts. In 11 grafts invasive angiography showed a significant stenosis > 50% (QCA: 83 ±15% diameter stenosis).

MR measurement of normal vs. stenosed grafts differed significantly between the two groups for mean flow reserve 3.33 ± 0.38 vs. 1.26 ± 0.16 (p<0.001), mean velocity reserve 2.95 ± 0.31 vs. 1.13 ± 0.15 (p<0.001) and peak velocity reserve 1.77 ± 0.11 vs. 1.24 ± 0.19 (p<0.05).

Conclusions: MR breath hold flow measurement provides hemodynamic assessment of coronary grafts. Using adenosine flow and velocity reserves can be calculated. These noninvasively derived values are reliable in discriminating diseased from patent grafts.

RESTENOSIS AND GENETICS

P1060 Platelet glycoprotein IIIa polymorphism is not associated with increased percutaneous coronary intervention risk

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Background: Platelet aggregation has a role in the emergence of complications after PCI. Genetic polymorphism (PlA2) of the IIIa protein is associated with increased risk of endovascular thrombosis, stroke, and myocardial infarction. The role of this type of genetic heterogeneity in ischemic events during and after PCI has not been investigated.
Patients and Methods: Patients undergoing PCI (n=200) were enrolled. PCI was performed blinded to PlA2 status. The use of IIb/IIIa inhibitors was left to operator choice. Presence of polymorphism was correlated with baseline and events after PCI.
Results (table): The normal (A1A1), heterozygote (A1A2) and homozygote (A2A2) variants were found in 144 (72%), 55 (27.5%), and 1 (0.5%) respectively.

	A1A1 (n=144)	A1A2 (n=55)
Patients and PCI Characteristics		
Acute coronary syndrome	98 (68%)	36 (66%)
Platelet count (X1000/mm^3)	212±73	220±84
Heparin (IU)	5556±1580	6160±2511
Maximal ACT (sec)	266±60	281±58
IIbIIIa inhibitors	38 (26%)	14 (26%)
Base-line platelet aggregation units	166±44	174±50
Adverse Events		
No flow/thrombus	2 (1%)	0 (0%)
Any CPK-MB elevation (>X1)	56 (39%)	21 (38%)
CPK-MB elevation (>X3)	25 (17%)	7 (13%)
CPK-MB elevation (>X5)	14 (10%)	6 (11%)
MACE (death, MI, TVR) at 30 days	5 (3.9%)	0 (0%)

p=non-significant for all variables

One-year follow-up will be available.
Conclusions: In the present study: 1. The IIIa protein genetic heterozygote polymorphism (PlA2) is frequent (30%) in patients undergoing PCI, but the homozygote variant was very infrequent (0.5%). 2. The presence of PlA2 genetic polymorphism has no influence on clinical and angiographic presentations. 3. The presence of PlA2 genetic polymorphism has no influence on procedural outcomes, occurrence of complications, or 30-day events.

P1061 Apolipoprotein E genotype predicts the clinical outcome after coronary artery stenting

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Background: The T allele of the -219G/T polymorphism and the epsilon 4 allele of the gene encoding apolipoprotein E were found to be associated with an increased risk of coronary artery disease. We examined whether these alleles were also related to adverse clinical and angiographic outcomes after coronary artery stenting.
Methods: In 1850 consecutive patients, the occurrence of myocardial infarction (MI), target vessel revascularization (TVR), and the combined incidence of death, MI, or TVR (= MACE; major adverse clinical events) were evaluated over 1 year after stenting. Repeat angiography at six months was achieved in 84.1% of the patients; angiographic restenosis was defined as a 50% or greater diameter stenosis at follow-up.
Results: The incidences of MI, TVR and MACE were significantly lower among carriers of the -219T allele, with patients of genotype TT having the lowest risk (Table). In contrast, the risk of MI, TLR or MACE was not related to the presence or absence of the epsilon 4 allele (Table). The rate of angiographic restenosis was equally distributed between the carriers of genotype -219GG (35.0%), GT (32.5%) and TT (31.6%) (P=0.6) and between carriers of allele epsilon 4 (34.1%) and patients not carrying allele epsilon 4 (29.7%) (P=0.1).

	-219GG	-219GT	-219TT	P value	epsilon 4	not epsilon 4	P value
MI (%)	3.2	1.5	1.1	0.03	2.1	1.2	0.24
TVR (%)	24.3	20.2	16.2	0.008	21.0	18.5	0.24
MACE (%)	27.2	24.6	19.6	0.02	23.6	20.3	0.14

Clinical outcome 1 year after coronary artery stenting

Conclusions: Contrary to our expectations, the -219T allele of the apolipoprotein E gene was associated with lower degrees of MI, TVR, and MACE after coronary stent placement. The epsilon 4 allele was not significantly related to the clinical and angiographic outcome after stenting.

P1062 Oestrogen receptor-α polymorphisms and angiografic outcome after stented angioplasty: a comparison between postmenopausal women and men

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The angiographic outcome after coronary stenting seems to be similar between genders. Most women undergoing percutaneous coronary intervention are postmenopausal and older than men. Female hormones play a role in the occurrence of coronary disease in women, but the effects in males are less known. Estrogens activity is mediated by the interaction with specific receptors located in various organs and tissues such as endothelial and vascular smooth muscle cells of both, women and men. In this study we have tested the role of two alfa-estrogen receptor (ER) gene polymorphisms, PVU and Xba, in the occurrence of in-stent restenosis (ISR).
Methods and Results: The 6-month angiographic outcome of 719 stented lesions was assessed in 136 PM-women (PMW) and 510 men. PMW were older (65±8 vs 61±9, p=0.001), showed a worse risk profile (diabetes p=0.0001, hypertension p=0.0001 and hypercholesterolemia, p=0.02) and had smaller vessel diameters (2.75±0.5 vs 2.9±0.5 mm, p=0.001). The global restenosis rate was 28.1%. A higher incidence of ISR was observed in PMW compared to men (35.6% vs 26.1%, p=0.02).
The restenosis rate for women and men according to the PVU-ER polymorphisms were: PVU-C/C= 32 vs 20.7%, p=0.2; PVU-C/T= 32.5 vs 27.2%, p=0.3; PVU-T/T= 43.9 vs 28.2%, p=0.05. Analysis of restenosis for the Xba polymorphism in PMW and men was: Xba-1/1= 41.2 vs 21.3%, p=0.09; Xba-1/2= 33.3 vs 27.2%, p=0.3; Xba-2/2= 37 vs 27.8%, p=0.1.
Although PMW tended to higher ISR rates for each genotype, the highest ISR rate was associated with the T/T polymorphism of the PVU genotype in females compared to males.
Conclusion: Common risk factors such as diabetes and hypertension together with the smaller vessel size may account for a higher incidence of ISR in our series of PMW compared to men. While ISR was similarly distributed according to the ER polymorphism among men, ISR in TT homozygous women was higher, suggesting that ISR may be in part modulated by this polymorphism in women but not in men.

P1063 Age dependent impact of the 894 TT genotype of the endothelial nitric oxide synthase on the outcome of men following coronary stent placement

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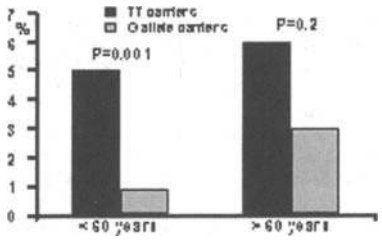
Background: The functional 894G/T endothelial nitric oxide synthase (eNOS) polymorphism has been found to be clinically relevant, with the TT genotype as a risk factor. Since the relative contribution of genetic factors may decrease with age and may be more pronounced among younger men, we performed a specific analysis for male patients with coronary artery disease undergoing coronary stenting.
Methods: We analysed 1459 consecutive men, there were 620 patients < 60 years and 839 patients > 60 years. One-year mortality was the primary endpoint of the study. The combined incidence of death and myocardial infarction (MI) during the first year was also assessed. Odds ratios (OR) and respective 95% confidence intervals associated with the carriage of the 894TT e NOS genotype are shown.
Results: The 894TT eNOS genotype was associated with a significant risk increase for death within 1 year only among younger patients (figure). In patients < 60 years, the mortality was 5.7% in TT-carriers vs 0.9% in G-allele carriers (OR, 6.4 [2.1 to 20.1], P=0.001.) The difference was much less evident in patients > 60 years, with a mortality of 6% in TT-carriers and 3% in G-allele carriers (OR, 1.9 [0.77 to 5.10], P=0.2). It remained also true for the combined 1-year incidence of death and MI: it was 8.6% vs 2.6% (P=0.007) for younger men and 7.2% vs 4.3% for older men (P=0.3), among TT-carriers and G-allele carriers, respectively.



1 year mortality after coronary stenting.

Conclusions: The 894TT genotype can serve as a prognostic marker of an unfavourable outcome after coronary stenting, especially among young men.

P1064 Endothelial nitric oxide synthase E298D gene polymorphism and restenosis after percutaneous coronary intervention

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Background: Nitric oxide (NO) is a potent vasodilator and has important antiproliferative effects. Some endothelial NO synthase gene polymorphisms may influence plasmatic and intramural NO concentrations. Thus, they may play an important role in pathogenesis of coronary atherosclerosis and in restenosis.
Aim OF THE STUDY: To assess the occurrence of restenosis and loss of lumen diameter after percutaneous coronary intervention (PCI) according to the genotype of E298D polymorphism (Glu-298-Asp) in exon 7 of endothelial NO-synthase gene in patients with coronary artery disease (CAD).
Methods: We studied 96 patients with CAD (age 36-79 years, average 57±9), who had repeated coronary angiography for suspected clinical restenosis and signed informed consent for DNA analysis. Restenosis was evaluated by quantitative coronary angiography (QCA) by using GE OEC CRS-PC software in corresponding views. Restenosis was considered as 50% or more severe stenosis of reference lumen within the site of intervention. In addition, absolute and relative late loss of lumen diameter were evaluated by comparison with QCA result obtained immediately after the procedure.
Results: Genotype frequency was 7%, 51%, and 42% for DD, ED, and EE genotypes, respectively. The restenosis rate was 71% in DD genotype, 37% in ED genotype and 25% in EE genotype ($p < 0.05$). In addition, the absolute and relative late loss were also significantly higher in DD homozygotes (1,3±0.9 mm, 46,5±37,0%), as compared to ED heterozygotes (0,8±0,7 mm, 31,2±30,0%) and EE homozygotes (0,5±0,4 mm, 17,7±22,1%) ($p < 0,05$). The results were also significant when EE homozygotes were compared to other genotypes.
Conclusions: The D allele homozygotes of E298D polymorphism of NO synthase gene have significantly higher frequency of restenosis and, more importantly, late lumen loss as compared to heterozygotes and E allele homozygotes. The lowest restenosis rate and late loss were associated with EE genotype. These pilot study results need to be validated by larger series of patients.
(supported by grants: IGA MZ CR NA 5613-3, LN00B107 MSMT CR, Center of genomics CR LN 00A79 and MS MT CR 206017-01)

P1065 β2-Adrenergic receptor polymorphism THR164ILE is an independent predictor of severe coronary artery disease

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Background: Beta2-adrenergic receptor (b2AR) polymorphism (poly) determines functional cardiac responses to catecholamines and adversely affects the outcome in patients (pts) with congestive heart failure. Furthermore, several studies showed that b2AR poly affects bAR mediated vasodilation. Therefore, we studied two poly of the b2AR, the GLN27GLU and the THR164ILE, that impair cardiovascular responses, in pts with severe coronary artery disease (CAD) undergoing percutaneous coronary interventions (PCI).
Methods: Study group consisted of 200 consecutive pts (CAD pts) (166 men; 60±11 years) undergoing PCI in our Cath Lab. The control population consisted of 100 healthy volunteers blood donors. All clinical, echocardiographic and angiographic characteristics of study group were determined. At time of PCI, peripheral blood was drawn to determine b2AR genotype by restriction fragment length poly. One hundred forty seven pts completed at least 6 months follow-up period (7±2 months) and any major adverse cardiac event (MACE) (including cardiac death, new acute myocardial infarction, re-PCI of target vessel or CABG involving treated segment) was checked and recorded in a database.
Results: There were no differences in the frequency of the b2AR 27 poly compared to our control population. However in CAD pts the frequency of heterozygous THR164ILE (164 HET) was threefolds higher than the control group (14% vs 3% respectively, $p<0.001$). No homozygous for ILE 164 were found. We did not observe any difference in terms of clinical, biochemical, echocardiographic and angiographic parameters of the 164 HET pts that could be major causative for CAD. The Kaplan-Mayer curves for event free survival showed a significant higher risk for 164 HET pts of combined death and new acute myocardial infarction ($p=0.0193$) and total MACE ($p=0.039$). Furthermore, at a Cox regression analysis the 164 HET was an independent predicting factor for total MACE ($B=1.185$, $p=0.015$) and there was no interaction noted for this relationship considering age, risk factors, number of vessel treated, and b2AR 27 poly.
Conclusion: We conclude that polymorphism of the b2AR in position THR164ILE is an independent predictor of adverse clinical outcome in CAD pts.

P1066 Interleukin-10 and tumor necrosis factor gene polymorphisms and thrombotic and restenotic events after coronary stenting

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Background: Inflammatory mechanisms have been shown to play an important role in the process of restenosis after percutaneous coronary interventions. Cytokines IL-10 and TNF-alpha exert opposite effects in inflammatory reaction. Functional single nucleotide polymorphisms located inside or close to the genes of IL-10, or TNF-alpha, and TNF-beta have an influence on gene expression and plasma levels of IL-10 or TNF-alpha, respectively. In this study we assessed the influence of IL-10, TNF-alpha and TNF-beta polymorphisms on restenotic and thrombotic events.
Methods: In a population of 1850 consecutive patients, we assessed the incidence of death, myocardial infarction (MI), clinical restenosis (target vessel revascularisation) and angiographic restenosis (>=50% diameter narrowing at follow-up angiography performed in 84% of patients) over 1 year after coronary stenting. Genotyping was performed with techniques based on the polymerase chain reaction.
Results: The polymorphisms in the IL-10 promotor (-1082G/A, -819C/T, and -592C/A), in the TNF-alpha promotor (-863C/A and -308G/A) and TNF-beta intron 1 (252G/A) were neither associated with the incidence of angiographic restenosis nor thrombotic events. We further analysed three IL-10 haplotypes (-1082/-819/-592 - ACC, ATA, GCC) and four TNF haplotypes (-308/-863/252 - ACG, GAA, GCA, GCG). No relevant relationship was observed between the studied IL-10 and TNF haplotypes and the incidence of adverse events (see Table).

TNF and IL-10 haplotypes

	TNF					IL-10			
Haplotypes	ACG	GAA	GCA	GCG	p	ACC	ATA	GCG	p
Angiographic restenosis	32%	33%	34%	31%	0,24	33%	33%	33%	0,88
Clinical restenosis	20%	18%	21%	19%	0,08	20%	21%	20%	0,75
Death or MI	5%	3%	5%	3%	0,13	4%	4%	5%	0,14

Incidence of adverse events and TNF and IL-10 haplotypes

Conclusion: These findings suggest that six functionally relevant polymorphisms of IL-10, TNF-alpha and TNF-beta are neither separately nor in combination associated with the risk of restenotic and thrombotic events after coronary stenting.

P1067 The endothelial nitric oxide synthase (eNOS) gene polymorphism (Glu298Asp) is associated with coronary in-stent restenosis

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Background: The biological effects of endothelium-derived Nitric oxide (NO) include vasodilation, inhibition of vascular smooth muscle cell growth, antiatherogenic property, prevention of platelet aggregation and adhesion of white cells to the blood vessel wall. Reduced or impaired synthesis of NO promotes vascular smooth muscle cells proliferation and thus may induce neointimal hyperplasia leading to coronary in-stent restenosis. The Glu298Asp variant of eNOS gene is functional with the Asp allele being associated with hypertension, myocardial infarction, coronary spasm and atherosclerosis. In this study, we have examined the effect of this allele on risk for in-stent restenosis.
Methods: 226 consecutive patients who underwent elective coronary artery stenting to de novo lesions in native coronary arteries were prospectively studied. Patients were restudied with coronary angiogram at 6 months and the stented lesions were assessed with automated quantitative angiography system. Coronary in-stent restenosis was categorically defined with the classic criterion of >50% diameter stenosis at follow up. Genotype was determined by PCR and restriction enzyme digestion with DpnII.
Results: In the 206 (91.15%) patients who were restudied angiographically at 6 months the binary restenosis rate was 30.1%. Overall, genotype distribution was in Hardy-Weinberg equilibrium and the frequency of the Asp allele was 0. 33 (95%CI: 0.28-0.38). Compared to 298Glu homozygotes, carriers of the 298Asp allele showed a higher frequency of restenosis with odds ratio of 2.0 (95% CI: 1.08-3.73, p= 0.026).
Conclusion: In coronary artery disease patients, the possession of 298Asp allele is a risk factor for coronary in-stent restenosis, demonstrating the importance of the NOS system in restenosis.

P1068 FcgammaRIIa-R-H131 polymorphism is associated with the formation of restenosis after coronary stenting

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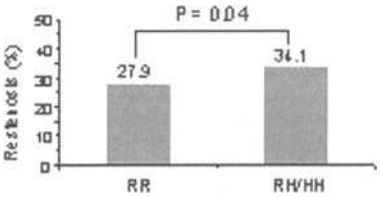
Background: IgG Fc receptor FcgammaRIIa-R-H131 polymorphism has a significant influence on human IgG2 binding to this receptor. A single nucleotide substitution (G507A) causes the amino acid exchange, Arg (R)-His (H) at position 131. FcgammaRIIa-H/H131 interacts well with human IgG2 whereas FcgammaRIIa-R/R131 binds IgG2 poorly. Conversely, the opposite affinities are true for binding of C-reactive protein (CRP). Inflammation is thought to play a role in the formation of neointima.
Methods: FcgammaRIIa-R-H131 genotypes were determined with polymerase chain reaction and allele-specific probes (Taq Man). Due to differences in nucleotide sequence between the FcgammaRII genes A, B and C in proximity to the polymorphic base it was possible to construct allele and gene (gene A) specific probes. Consecutive patients (n=1850) that underwent coronary stent implantation due to symptomatic coronary artery disease were included in the study. Six-month follow-up angiography was performed in 84% of the patients.
Results: The genotype distribution of the patients was 18.3% (R/R), 47.2% (R/H), 34.5% (H/H) and complied with Hardy-Weinberg equilibrium. The incidence of restenosis was 34.1% for H carriers vs. 27.9% for RR patients which results in a significant increase (by 34%) of the risk of restenosis for H allele carriers (Fig. 1).



Conclusions: Homo-and heterozygous carriers of FcgammaRIIaH131 have an increased risk of restenosis following coronary stenting. This new finding provides additional cues on the role of inflammation and immunomodulation in the process of restenosis.

P1069 Rat aortic stenting: a simple model of in-stent restenosis

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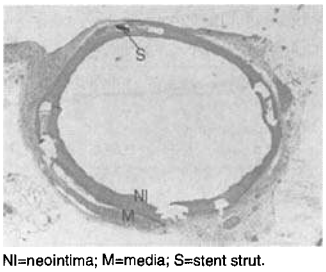
Background - In-stent restenosis (ISR) occurs in 10-21% of the patients who have undergone a percutaneous coronary intervention with placement of a stent. Several drugs are being investigated in animal models to test their efficacy for treatment of ISR. The currently available models are limited in number, elaborate and expensive.
We have developed a simple and inexpensive rat model, in which new therapies for ISR can be easily tested.
Methods: Male Wistar rats (400 to 425 grams) were anaesthetised with the use of N2O, O2, and isoflurane gas narcosis. The lower 2.5 cm-segment of the abdominal aorta was prepared free very carefully from the vena cava. Two vascular clips were placed to isolate a 2 cm-segment. A small incision was made and the isolated aortic segment was stented with a human coronary stent (Medtronic beStent, 2.5 x 10 mm). The incision was closed with a 9-0 suture, and the clips were removed. Rats were killed after 14, 21, or 56 days, and the consequences of stent placement were studied.
Results: After 14 days, neointima formation was minimal and only partial, but after 21 and 56 days a prominent, concentric neointima had been formed. On the luminal side of the neointima, histological patterns that are typical for cell division were seen in all three groups.
Conclusion: Placement of a human coronary stent in the rat abdominal aorta results in a clear and fulminent in-stent restenosis within one month. In accordance with the pig coronary stenting model, cell division is still observed even after 8 weeks. Therefore, the new rat abdominal aorta model is a simple, promising method to investigate the efficacy of oral drugs or drug-eluting stents for treatment of ISR.



NI=neointima; M=media; S=stent strut.

P1070 Smoking and restenosis after coronary artery stenting: the artefact of smoker's paradox

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Background: Cigarette smoking is a strong risk factor for heart disease. Some previous studies showed a lower incidence of adverse events and restenosis after percutaneous coronary interventions (PCI) in smokers which has since been called the "smoker's paradox". We investigated the influence of smoking on restenosis after stenting. Methods: A consecutive series of 6911 patients who underwent coronary artery stenting was analysed. The follow-up protocol included 6-month angiography (performed in 80% of the patients) and a contact of 12 months after the procedure. Primary endpoint of the study was angiographic restenosis defined as a > 50% diameter stenosis at follow-up. Other endpoints were the combined rate of death and myocardial infarction and the need for reinterventions at 1 year. Results: As shown in the table, the risk profile of the smokers is significantly different from that of non-smokers. Apparently, smokers have a lower risk of restenosis. However, the risk reduction disappears after adjustment for baseline characteristics: adjusted odds ratio, 0.94 [95% CI, 0.81-1.09]. More importantly, smokers showed a significantly increased risk of death or myocardial infarction (adjusted hazard ratio, 1.29 [95% CI, 1.03-1.61].

Univariate Analysis

	Smokers (n=1848)	Nonsmokers (n=5063)	p
Age, years	59 ± 11	67 ± 10	<0.001
Women, %	16	27	<0.001
Diabetes, %	15	22	<0.001
Multivessel disease, %	67	75	<0.001
Vessel size, mm	3.06 ± 0.51	3.00 ± 0.54	<0.001
Angiographic restenosis, %	28	31	0.04
Reinterventions, %	17	19	0.13
Death or MI, %	6.4	6.9	0.54

Conclusions: The apparent relation between smoking and a lower restenosis rate after PCI is the consequence of more favourable baseline characteristics. Smoking itself has an unfavourable influence on the outcome after stenting by increasing the risk of most dreadful events.

P1071 Circulating IgM and IgG cardiolipin antibodies in restenosis after balloon angioplasty and their interference with prothrombotic pathways

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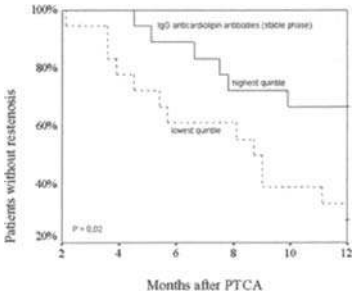
It was our aim to show the possible role of circulating IgM and IgG anticardiolipin (aCL) antibodies for the development of restenosis. Furthermore, we were interested in the interference of aCl antibodies with parameters of different prothrombotic pathways.
We investigated 145 patients with stable coronary artery disease after a successful angioplasty for their plasma levels of IgG and IgM aCL antibodies. Sixty-six patients (45%) developed angiographically proven restenosis, seventeen of them (12%) developed more than one episode of restenosis.
ACL IgM antibodies in the upper quartile at baseline (before angioplasty) predicted a higher risk to suffer from recurrent restenosis compared to the lowest quartile (R= 0,04) and were positively correlated with Lipoprotein (a) (P=0,04). In contrast, also aCL IgG antibody levels in the lowest quintile at baseline conditions in chronic stable disease were a risk factor for restenosis (P=0,01). Adjusting for cardiovascular risk factors, low aCL IgG antibodies represented an independent risk factor for restenosis (P= 0,036). Kaplan-Meier survival analysis showed a higher event rate in patients with low aCL IgG antibodies (P= 0,02; Fig. 1). ACL IgG antibodies were further correlated with PAI-1 activity after angioplasty (P= 0,021).
In conclusion, high aCL IgM antibodies seem to be a risk factor for a more complicated course of disease with a tendency to recurrent restenosis after PTCA whereas low aCL IgG antibodies are more likely an independent risk predictor indicating a protective effect against the development of restenosis. Associations of aCL IgM antibodies with Lipoprotein (a) and with aCL IgG antibodies with PAI-1 activity might further explain their suspected role in thromboembolic diseases.



P1072 Doxycycline-therapy reduces angiographic restenosis rate after percutaneous coronary intervention in non-diabetic smoking males

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The potential role of Chlamydia Pneumoniae in the pathogenesis of coronary artery disease remains to be a matter of controversial discussion. Goal of this study was to test the influence of antibiotic therapy on clinical outcome and restenosis rate (RR) after percutaneous coronary intervention (PCI).

Methods: We followed 1.019 patients with consecutive PCI at Red Cross Hospital Cardiology Center. The treatment group (TG) consisted of 541 consecutive patients (7/98 to 10/98) receiving doxycycline (100mg/day) for 50 days after PCI; the control group (CG) consisted of 478 patients with standard treatment (250 consecutive patients, 5/98 to 7/98; 228 consecutive patients, 10/98 to 11/98). Baseline demographics were equally distributed: mean age (TG: median 65 years; 25th percentile (P), 58 years; 75th P, 72 years versus CG: median 64 years; 25th P, 56 years; 75th P, 71 years), smoking (20.8% vs 20.9%), diabetes (22.9% vs 22.0%), dyslipidaemia (52.2% vs 51.2%), and hypertension (46.0% vs 41.2%). The percentage of women was higher in TG (TG, 30.1% vs CG, 22.6%; $p<0.01$). Clinical follow-up (FU) was assessed equally after 7 months (median, 237 days; 25th P, 223 days; 75th P, 272 days) and obtained in 614 patients (60.3%). Angiographic FU was higher in TG (64.5% vs 56.0%). This carried the risk of underestimating RR of TG relative to CG, thus favoring the acceptance of the antibiotic hypothesis. To exclude this potential error, RR was calculated as the ratio of restenotic patients to all patients.

Results: No difference between TG and CG was found in adverse event rates (respectively, MI: 0.7% vs 1.3%; Re-PCI: 24% vs 20.9%; coronary artery bypass graft: 5% vs 3.9%, death at 6 months 3.5% vs 2.1%) and RR (21.6% vs 23.4%). Subgroup analysis of smoking nondiabetic males (TG, n=59; CG, n=55) showed a significantly lower RR in TG (10.9% vs 30.5%; $p<0.02$) without differences in clinical outcomes.

Conclusions: Treatment with 100mg doxycycline over 50 days after PCI does not appear to influence clinical results and over all restenosis rate. The observed reduction in RR among doxycycline-treated nondiabetic male smokers deserves further investigation.

P1073 C-reactive protein stimulates smooth muscle cell proliferation but does not affect endothelial tissue factor activity or endothelin-1 release

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Background: Increased levels of C-reactive protein (CRP) are predictive of adverse coronary events in stable and unstable angina. Furthermore, elevated levels of CRP are predictive of both early and late complications, including restenosis, after coronary angioplasty and stent implantation. The mechanisms responsible for these complications are not clear but involve endothelial injury and smooth muscle cell proliferation. CRP has been found within atherosclerotic plaques and has been shown to increase the expression of adhesion molecules and the production of chemokines from endothelial cells. We therefore investigated the effect of CRP on vascular cells.

Methods and Results: Human recombinant CRP and human serum high purity CRP was tested on human internal mammary artery smooth muscle cell (HIMASMC) proliferation and also on tissue factor (TF) activity and endothelin-1 (ET-1) release from bovine aortic endothelial cells (BAEC). All experiments were performed on 2 or 3 separate occasions. Incubation for 96h with 100μg/ml CRP increased HIMASMC proliferation by 42% (n=6, $p<0.01$). This effect on HIMASMC proliferation was also present at 10μg/ml CRP (n=9, $p<0.01$), with a concentration-dependent increase up to 100μg/ml. At 5μg/ml CRP, there was no significant increase in HIMASMC proliferation. Incubation with 10μg/ml CRP and 10ng/ml recombinant tumor necrosis factor alpha showed no additional increase in HIMASMC proliferation. There was no effect of 100μg/ml CRP on TF activity or ET-1 release from BAEC incubated for up to 24h, with or without serum.

Conclusions: These results show for the first time that CRP stimulates HIMASMC proliferation and elucidates a possible role for CRP in the pathogenesis of restenosis. In this study, CRP did not affect endothelial function as assessed by TF activity and ET-1 release.

P1074 Inhibition of smooth muscle proliferation by glycoprotein IIb-IIIa antagonists in vitro: eptifibatide more effective than abciximab or tirofiban

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Background: Recent data suggest that among the platelet glycoprotein (GP) IIb-IIIa (alpha IIbeta,beta3) integrin antagonists not only abciximab (ReoPro®, a chimeric monoclonal antibody), but also eptifibatide (Integrilin®, a cyclic heptapeptide) is able to bind to integrin-receptors of the alpha nu subunit family, whereas the affinity of tirofiban (Aggrastat®, a peptidomimetic) is restricted to alpha IIbeta,beta3. We were interested whether these differences in integrin specificity might influence human smooth muscle cell (SMC) migration and/or proliferation in vitro.

Methods: A two-dimensional assay system for determination of SMC migration/ proliferation was used. Sterilized steel supports were inserted into gelatine coated six well plates. Human umbilical artery SMC were seeded into the middle hole of each support. At confluency, inserts were removed and after 24 hours of serum deprivation, GP IIb-IIIa antagonists were added in culture media with 10% calf serum. After 20 days cell-layers were stained, digitally quantified (Scion Image) and in parallel cells counted.

Results: No GP IIb-IIIa antagonist influenced SMC area significantly at therapeutic plasma concentrations (abciximab: 200 ng/ml; eptifibatide: 2 μg/ml, tirofiban: 40 ng/ml). At 10x conc. eptifibatide reduced SMC area significantly by 30% ($p=0.01$) and at 30x conc. by 41% ($p=0.001$), whereas abciximab and tirofiban showed no significant influence. This effect was paralleled by a decrease in cell counts (30x conc.: 43% reduction, $p=0.005$), reflecting an inhibition of cell proliferation.

Conclusions: Among the currently available GP IIb-IIIa antagonists, only eptifibatide showed a dose-dependent inhibition of SMC proliferation in our in vitro assay system. Abciximab and tirofiban exerted no significant effects. As these findings might be due to eptifibatides broader range of integrin specificity (alpha IIbeta,beta3 and various alpha nu subunit integrins), compared to abciximab (alpha IIbeta,beta3 and alpha nu,beta3) or tirofiban (only alpha IIbeta,beta3) we hypothesize that inhibition of SMC proliferation requires simultaneous blockade of several integrin receptors. The clinical relevance of this phenomenon, with reduction of late restenosis after percutaneous coronary interventions needs to be proven.

P1075 Intracoronary paclitaxel added to contrast media inhibits in-stent restenosis of porcine coronary arteries

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Objective: Coronary arteries are coated with contrast media forming a thin film on the endothelium during catheterization. In a prior study, we demonstrated that a taxane dissolved in a contrast medium can inhibit in-stent restenosis at subtoxic systemic taxane levels. The present study was designed to test the efficacy of different formulations of Paclitaxel added to the contrast agent Iopromide in a porcine stent model.

Methods: 34 stents were implanted into LAD and CX coronary arteries of 17 pigs using an 1.2 to 1 overstretch ratio. Iopromide-370 was used in group I (control), the treatment groups were injected with 80 ml intravenous Iopromide plus 12.8 mg Paclitaxel (group II), 80 ml intracoronary Iopromide plus 6.4 mg Paclitaxel (group III), and 80 ml intracoronary Iopromide plus 12.8 mg Paclitaxel respectively (group IV). Quantitative coronary analysis (QCA) was used to evaluate measures of restenosis (reference diameter, minimal lumen diameter, diameter stenosis) from the pre-sacrifice angiography at 28-day follow-up.

Results: QCA documented no differences between the baseline parameters of the four groups. At follow-up, however, there was a marked reduction of all parameters relevant to in-stent restenosis in favor of the intracoronary Iopromide-Paclitaxel administration (see table).

Quantitative coronary angiography

	group I	group II	group III	group IV	p
# of pigs	6	3	4	4	
# of stented vessels	12	6	8	8	
reference diameter	2.8±0.2 mm	2.7±0.2 mm	2.7±0.5 mm	2.7±0.2 mm	0.976
minimal lumen diameter	1.1±0.3 mm	1.3±0.5 mm	1.7±0.8 mm	2.0±0.5 mm	0.004
diameter stenosis	59±9%	55±15%	38±19%	29±13%	0.001

Conclusion: This study provides evidence that intracoronary application of a taxane dissolved in a contrast medium can prevent in-stent restenosis. The novel drug delivery mechanism is efficient at subtoxic systemic levels of Paclitaxel. Thus, this simple and inexpensive approach is potentially suited for prevention of restenosis in a broad spectrum of interventional cardiology.

PAEDIATRIC CARDIOLOGY, OTHERS

P1076 Ventricular septal defect – A review

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Ventricular septal defect(VSD) is the most commonly encountered congenital heart lession, occurring in more than 20% of CHD.
Objective: to determine the frequency of VSD in our cardiology patients, including clinical forms, haemodynamic profiles as well as the outcome.
Materials and methods: Using non-invasive techniques (history, clinical examination, chest X-ray, ECG and Doppler echocardiography, the CHD diagnosis has been established in patients examined in University Children's Hospital, including in and outpatients.
Results: Of 665 children with CHD,247 (37%)had VSD: 206 (30.9%) as a solitary lession, 27 (4.0%) in combination with other defects, mainly with ASD and 14 (2.1%) as a part of complex congenital heart disease.VSD was found slightly more frequently in females (53.5%) as compared to males 946.5%). VSD was the most common CHD in the majority of chromosomal syndromes (21-trisomy).
Clinical forms, haemodynamic changes and the outcome are prescribed below:

– muscular VSD	21 (8.6%)
– restrictive	115 (46.5%)
– nonrestrictive	66 (26.7%)
– in spontaneous closure	28 (11.3%)
– in pulmonary hypertension	17 (6.9%)
Total	247 (100%)

All children were followed-up by cardiologists and, when needed, have given adequate, anticongestive therapy including digoxin, furosemide, ACE inhibitors, spironolactone.
They also followed AHA recommendations for the prevention of infective endocarditis. However,in one, five yrs old child with small, restrictive VSD severe infective endocarditis occurred including severe tricuspid regurgitation.
This child was born abroad and since the VSD was small the decision was made to don't be operated but to be in a continuous infective endocarditis prophylaxis.
After her comming back, 1 mo after a dental procedure (no prophylaxis was used) she got endocarditis which was very refractare to antibiotic therapy.
From at least 83 pts with VSD who require cardio-surgery treatment, only 17 have been operated abroad, since our region has no cardio-surgery center.
Conclusion: In our region echocardiography as a very precise diagnostic tool is mainly sufficient for the diagnosis of CHD. The big problem is lack of cardio-surgery; so a certain number of patients with operable VSD is older then 10 years.On the other hand infective endocarditis is also a problem in cases with restrictive VSD.

P1077 Dimensions of the pulmonary arteries and some cardiovascular structures in children and young adults with tetralogy of Fallot

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The results of complete correction of tetralogy of Fallot are closely related with its anatomy. Our study is undertaken to obtain new information for the anatomy of the childrens and young adults with tetralogy of Fallot.
Methods: Diastolic diameters of the right and left pulmonary arteries and their lower lobe arteries, descending thoracic aorta, right ventricular infundibulum, pulmonary valve anulus, pulmonary trunkus were estimated from angiograms in 22 children and young adults with tetralogy of Fallot and correlated with BSA and for each of them Mc.Goon and the Ratio, (the sum of the diameters of the lower lobe arteries divided with the diameter of aorta descendens)is calculated.
Results: Compared with normal subjects patients with tetralogy of Fallot have smaller diameters of the above cardiovascular structures and different growth patterns. The median values of the diameters of the right ventricular infundibulum, pulmonary trunk, pulmonary annulus were 50% of the normal ones. The right pulmonary prebranching diameter and the right lower lobe artery is greater than the left but not significantly. Mc.Goon median value is 1,7 and Ratio value 1,2.
There is a strong correlation between aorta descendens and BSA, but there is no correlation between right ventricular infundibulum, pulmonary valve anulus, pulmonary trunkus right and left pulmonary arteries their lower lobe arteries with BSA and aorta descendens suggesting different growth patern.
Conclusion: Tetralogy of Fallot is a complicated congenital disease and the growth of the cardiovascular structures is different from normal subjects. There is severe obstruction at the level of the right ventricular outflow tract. The pulmonary arteries are good developed but even these are smaller then normal subjects. The new Index can be a more appropriate measure of pulmonary artery development, ignoring the mistakes rsulting by stenoses or dilatation of the main branches.

P1078 Degree of atherosclerotic involvement of primary congenital coronary anomalies

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There is no consensus about the subject that the coronary anomalies may cause the predisposition for atherosclerosis. In this study, it was determined whether the atherosclerotic involvement in patients with coronary anomalies was different from the patient group which the frequency of anomalies was investigated or not. The angiographic repots of the consecutive 2119 patients were screened and 15 patients with coronary anomalies were detected. The angiographic and ventriculographic data of the patients with coronary anomalies were compared witf the data of the patients without coronary anomalies. A numeric value was given to each segment of the vessel according to the decrease in percentage of the luminal diameter as taing into consideration of the 29 segment coding system of ACC/AHA. The coronary atherosclerosis score of that artery was found with the addition of the numerical values in the related coronary artery. Total coronary atherosclerosis score was obtained with the addition of the atherosclerosis scores of three coronary arteries. Total coronary atherosclerosis score (104±131 v 108±122), total LAD score (42±50 v 47±50), total Cx score (20±44 v 41±51), total RCA score (41±66 v 30±52) were not different statistically between groups. These data suggest that there was not any difference between the patients with coronary anomalies and the patients without coronary anomalies according to atherosclerosis development.

P1079 Ventilatory efficiency during exercise in patients with cyanotic congenital heart disease is related to the clinical outcome after surgery

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Most patients (pts) who underwent surgical repair for cyanotic congenital heart disease (CCHD) are clinically well when examined at rest, but a considerable number may complain of exercise intolerance at heavy exercise. The aim of the present study was to analyse ventilatory efficiency during exercise and correlate with the clinical outcome after surgery.
Methods: 78 pts with surgical repair of CCHD (mean age: 12.6 ± 2.3 years) were studied. 3 subgroups of pts formed the study group: 32 pts with repair for tetralogy of Fallot (TF), 23 pts after Senning operation for transposition of great arteries (S) and 23 pts with Fontan operation for functionally univentricular hearts (F). Pts were compared to 27 age-matched controls. Exercise testing was performed on a treadmill. Gas exhange was measured on a breath-by-breath basis with mass spectrometry. To assess the efficiency of ventilatory gas exchange during exercise, alveolar ventilation (VA) was calculated and subtracted from total ventilation (VE). The difference which reflects the physiological dead space ventilation (VD) was used as an estimate of the ventilatory efficiency.
Results: During exercise, VE, VA and VD were significantly ($P = 0.01$) elevated in the 3 pts groups compared to normal contols. VD was abnormally elevated in 47% of TF, 65% of TGA and 62% of F. This was associated with a steeper slope of VE vs VCO2. This correlated with hemodynamic sequels after surgery such as pulmonary regurgitation, residual pulmonary stenosis and cardiomegaly after TF repair, severe right ventricular dilatation, tricuspid incompetence after S operation and atrioventricular valve insufficiency in F.
Conclusion: Assessment of ventilatory efficiency during exercise gives useful complementary information to other clinical tools to assess the functional outcome after surgery, since abnormal values correlated with hemodynamic sequels after surgery.

P1080 QP/QS ratio evaluation by phase veloecity cine magnetic resonance imaging in patients with left to right shunt

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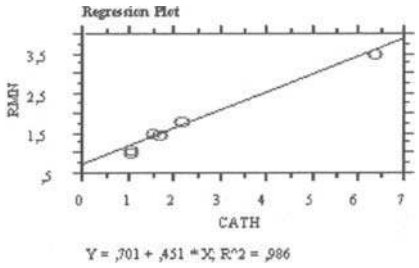
Objectives: : PVC-MRI is a powerful noninvasive technique to quantitate and analyze blood flow. Our purpose is to correlate QP/QS ratio evaluated by PVC-MRI and by cardiac cateterization (CC) in pts with septal defects or patent foramen ovale.
Methods: 7 pts with Atrial Septal Defect (3 pts), Ventricular Septal Defect (1 pt), Atrial Septal Defect + Anomalous Partial Pulmonary Venous Return (1 pt), Patent Foramen Ovale (1 pt), and suspected residual shunt in status/post closure of ASD by Ampatzer device (1 pt) have been evaluated by MRI and CC in order to calculate QP/QS ratio. 2 other pts have been excluded by the study because their turbolent flow at pulmonary artery level. The QP/QS ratio has been calculated by the oximetric method at CC, and measuring flows in pulmonary artery and aorta by PVC-MRI. Results have been analysed by means of a statistical-dedicated software (statwiew 4.5 for Mac).
Results: Linear regression analysis showed a high correlation between the two methods:

$y = 0.701 + 0.451*x$; $R^2 = 0.986$. p (ANOVA) < 0.0001.



Conclusions: Calculation of QP/QS ratio by PVC-MRI has a linear correlation with the oximetric method. Therefore PVC-MRI is an accurate, robust, and safe technique for obtaining in vivo blood flow information. Moreover PVC-MRI may be easily integrated into a comprehensive cardiac MRI evaluation that provide extensive diagnostic anatomical and functional information.

P1081 Plasma homocysteine levels and their reduction with folic acid/vitamin B6 in a cohort of apparently healthy young men in polish population

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Several cross-sectional and prospective studies have indicated that increased levels of total plasma homocysteine (tHCY) are an independent risk factor for cardiovascular disease.
The purposes of this study were to determine serum levels of tHCY and their associations with traditional risk factors of atherosclerosis and to assess the degree of tHCY reduction after two weeks administration of standard multivitamin tablets (containing folic acid and vitamin B6) in population of young, healthy Polish men.
In 150 men (mean age 20,5 ± 1,24 yrs) we evaluated clinical, anthropometric and biochemical measurements (tHCY, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, uric acid, apolipoproteins A and B). tHCY was determined with IMx analyzer and Abbot IMx TM Homocysteine Assay. 75 men (randomly assigned) started taking 1 tablet of Panvitan® for men (Bayer,USA) containing 0,2mg of folic acid and 3mg of vitamin B6 on the enrollment day. Concentrations of tHCY were measured at baseline and at two weeks in all subjects.
Mean concentration of tHCY in the studied group was 10,04 μmol/L (SD ±2,26 μmol/L). tHCY correlated with diastolic blood pressure values (r=0,208; p<0,03) and with uric acid concentrations (r=0,217; p<0,02). In the group administered with Panvitan® there was a reduction of mean tHCY level by 1,40 μmol/L (13,7%; p<0,01) compared with 0.61 μmol/L (6,2%, p<0,01) reduction in group with no supplementation. The reaction to Panvitan® was more pronounced in men with tHCY concentrations above 10 μmol/L.
Conclusion: Our data support the view that lowering homocysteine levels through dietary supplementation with folic acid and vitamin B6 may play an important role in reducing of cardiovascular risk.

P1082 Incubating arrhythmogenic right venticular cardiomyopathy in Naxos disease of childhood

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Background Arrhythmogenic right ventricular cardiomyopathy (ARVC) causes ventricular arrhythmias due to fibrofatty replacement of right ventricular (RV) myocardium. A deletion in plakoglobin (cell adhesion protein) in homozygous state results to ARVC (Naxos disease) 100% penetrant by adolescence. A study of homozygotes in childhood might elucidate the incubating period of ARVC.
Methods An affected family with 11 members was studied clinically and genetically. Three homozygous carriers for plakoglobin mutation were identified; two siblings (a brother, 13 years old and a sister, 5 years old) and their grandmother (58 years old). Cardiac biopsies were available in the two affected siblings.
Results ARVC was fully penetrant on ECG and echocardiography in the 13-year-old boy and his grandmother (2 major and 2 minor criteria). Endomyocardial biopsy of the boy revealed significant fibrofatty replacement of RV myocardium. The 5-year-old girl had complex ventricular extrasystoles mainly of RV origin (>10000/24h) without ECG or echocardiographic abnormalities. She died in severely progressive myelodysplasia 2,5 years later without developing any significant cardiac alteration. Postmortem gross pathology did not show any overt abnormality, but histology revealed tiny fibrosis with rare adipocytes in the subepicardial layers of RV free wall. Moreover there was diffuse subendocardial fibrosis. There was no inflammatory infiltration or leukemia infiltration.
Conclusions In this young child, ventricular arrhythmia was a striking feature although the ARVC pathological substrate appeared very mild. The early arrhythmogenicity might be attributed to the primary dysfunction of cell-cell adhesion.

P1083 Changes in aortic elasticity in non-operated Marfan patients after three years of follow-up

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Objective- Aortic elasticity is related to aortic rupture behavior and may serve as an additional risk factor. Aortic elasticity can be expressed in terms of distensibility and flow wave velocity, and is decreased in Marfan patients. The aim of this study was to determine changes in aortic elasticity assessed with MR imaging in non-operated Marfan patients.
Design and patients- In 2000, 19 consecutive non-operated Marfan patients (mean age 34 (8) years, 13 men and 6 women), who had undergone magnetic resonance (MR) imaging in 1996-1997, underwent second MR imaging. MR flow mapping was assessed at four levels (1: ascending aorta beyond the aortic root, 2: thoracic descending aorta, 3: descending aorta at the level of the diaphragm and 4: abdominal descending aorta) in the aorta. Distensibility and diameter at each level, and flow wave velocity (FWV) between levels were calculated.
Results- Mean time after first MR imaging was 38 (4) months (range, 34-49 months). No significant change in aortic diameter at any of the 4 levels was shown. Distensibility at second MR imaging at the ascending aorta (level 1) was significantly decreased (1.8 (1.0) 10-3 mmHg-1) compared to first MR imaging (2.7 (0.9) 10-3 mmHg-1, p<0.01). Accordingly, FWV in the aortic arch tended to be increased at second MR imaging (5.0 (1.2) m/s vs. 4.4 (1.0) m/s, p=0.10, respectively). At all other levels no changes in aortic elasticity were shown.
Conclusion- After 3 years of follow-up in non-operated Marfan patients elasticity in the ascending aorta was significantly decreased without changes in diameter. This finding could indicate that changes in aortic elasticity precede changes in aortic diameter in Marfan patients.

P1084 Correlation of plasma neurohormones and functional status in patients with right ventricular pressure and/or volume overload

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Objective: To examine the relation between plasma neurohormones Brain Natriuretic Peptide (BNP) and Atrial Natriuretic Peptide (ANP), and NYHA functional status classification, in patients with chronic right ventricular (RV) pressure and/or volume overload.
Methods: BNP and ANP levels were measured in 67 patients (age 30(12)) and 12 matched healthy volunteers (age 31(10)). Patients with congenitally corrected transposition of the great arteries (CCTGA, n=12), surgically corrected TGA (n=18), and subpulmonary pressure/volume overloaded RV (n=37), were classified in NYHA functional classes I - IV. Exclusion criteria included renal impairment, atrial arrhythmias and left ventricular dysfunction.
Results: Plasma BNP levels in asymptomatic patients (NYHA I) were significantly higher compared to healthy volunteers (5.0±4.0 vs 2.4±1.8 pmol/L, p=0.03). There was no significant difference in both BNP and ANP plasma levels between patients with functional class NYHA I vs NYHA II (BNP 5.0±4.0 vs 5.1±2.2 pmol/L; p=ns, and ANP 6.5±5.3 vs 5.9±3.2 pmol/L; p=ns). BNP and ANP plasma levels were significantly higher in patients with NYHA III compared to NYHA II (BNP 22.1±8.6 vs 5.1±2.2 pmol/L, p=0.0001 and ANP 17.8±10.2 vs 5.9±3.2 pmol/L, p=0.001) and NYHA IV compared to NYHA III, respectively (BNP 115.7±57.88 vs 22.1±8.6 pmol/L, p=0.005 and ANP 57±31.7 vs 17.8±10.2, p=0.02).
Conclusion: A strong relationship exists between the NYHA functional class and plasma neurohormonal levels. Plasma neurohormones and in particular BNP may be used for quantitative follow-up in patients with chronic RV pressure and/or volume overload.

P1085 Validation of four risk scores in patients undergoing off-pump coronary surgery: a United Kingdom multi-centre analysis of 2,223 patients

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Objective: Various risk stratification systems have been developed based mainly on patients undergoing cardiac surgery with Cardiopulmonary Bypass (CPB). This report attempts to assess the validity and applicability of the Parsonnet score, the EuroSCORE, the ACC/AHA system and UK CABG Bayes model in patients undergoing Off-Pump Coronary Artery Bypass (OPCAB) surgery in the United Kingdom (UK).
Methods: Data on 2,223 patients who underwent OPCAB in eight UK cardiac surgical centres were collected. Predicted mortality risk scores were calculated using the four systems and compared to the actual observed mortality. Calibration was assessed by Hosmer-Lemeshow (HL) test. Discrimination was assessed by calculating the Receiver-Operating-Characteristic (ROC) curve area.
Results: Out of 2,223 patients 30 (1.3%) died in hospital. For the Parsonnet score the HL test was significant ($P<0.001$) and the ROC area was 0.74. For the EuroSCORE the HL test was also significant ($P<0.01$) and the ROC area was 0.74. For the ACC/AHA system the HL test was non-significant (P=0.73) and the ROC area was 0.75. For the UK CABG Bayes model the HL test was also non-significant (P=0.87) and the ROC area was 0.81.
Conclusion: This study shows that the UK CABG Bayes model is well calibrated and provides good discrimination when applied to OPCAB patients in the UK. Amongst the other three systems, the ACC/AHA system is also well calibrated but its discrimination power was less than that of the UK CABG Bayes model. These data suggest that the UK CABG Bayes model is an appropriate risk stratification system to use for patients undergoing OPCAB in the UK.

P1086 Ebstein's anomaly and isolated tricuspid valve dysplasia: prenatal diagnosis, management and outcome

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Objective: A meta-ananlysis of the literature and a comparison with the results of a tertiary referral centre for paediatric cardiology and cardiac surgery. Included is a review of the diagnosis, management and outcome in cases of tricuspid valve dysplasia.
Patients: The diagnosis tricuspid valve anomaly was made 14 fetuses. Isolated Ebstein's anomaly occurred in 4 patients. One patient had Ebstein's anomaly associated with discordance of the great arteries, congenitally corrected transposition of the great arteries. Tricuspid valve dysplasia was encountered in 10 fetuses.
Results: In the group with Ebstein's anomaly (N=4) 2 fetuses died in utero at a gestational age of 29 and 36 weeks. Parents opted for compassionate care in one fetus which died at an age of 2 days. One patient with congenital corrected transposition of the great arteries is alive at an age of 9 years after receiving pulmonary artery banding, a partial cavopulmonal connection and a Damus-Kay-Stansel operation. In this group 2 fetuses had other hypoplasia of the lungs, of which one had a chromosomal anomalies (trisomy 18).
Conclusions: Patients with a prenatal diagnosis of Ebstein's anomaly or dysplasia of the tricuspid valve represent the most serious component of the spectrum of Ebsteins malformation. The very poor outcome is representative for this selected population and cannot be compared to patients in which the anomaly is detected in a later stage of life. Parental counselling of these patients can therefor not be based upon the natural history of these older patients. Prenatal diagnosis provides opportunities for in depth counselling of the parents before the medical and emotional complexities associated with the neonatal intensive care setting are encountered. Surgical procedures of tricuspid valve repair or replacement are offered for this anomaly but this option is almost exclusively provided for patients with a diagnosis in later life, as very few patients survive the prenatal period.

P1087 Structural congenital heart disease in diabetic pregnancies

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Objective: The purpose of this study was to evaluate whether the increased incidence of fetal cardiac abnormalities in diabetic mothers is significantly related to maternal diabetic control.
Methods: Medical records of women with (pre-)gestational diabetes mellitus during pregnancy between January 1988 and December 1998 were retrospectively studied in Yale New Haven Hospital, USA.
Results: In 32 fetuses(5,8%, group A) a congenital heart defect was detected at a mean gestational age of 27,9 ± 1,19 weeks. In 527 fetuses(94,2%, group B) no cardiac malformation could prenatally be detected. The severance varied from mild hypertrophic cardiomyopathy to transposition of the great arteries or hypoplastic left heart syndrome. The mean age of the mothers was 30,7 ± 0,87 (group A) versus 29,1 ± 0,77 years(group B), the mean duration of the diabetes was 11,5 ± 2,2 vs 10,9 ± 1,1 years, and the mean concentration of glycosylated hemoglobin A(HbA1c) was 9,79 ± 0,69% vs 8,14 ± 0,29% (p=0,034).
Conclusion: A significant difference in HbA1c was found in favour of the group of women where no cardiac malformation could prenatally be detected. As the techniques and knowledge of prenatal detection of cardiac lesions improves, more lesions will be detected. As long as the mechanism of high blood glucose levels on the period of organogenesis is not yet fully understood, a benefit should come from controlling the diabetes before and during pregnancy. The incidence of congenital heart defects among fetuses of diabetic mothers will then hopefully be reduced to the incidence of CHD in the general obstetric population.

P1088 Prenatal diagnosis of the fetus with a hypoplastic left heart syndrome: management and outcome

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Objective: To review our 13-year experience with prenatally detected hypoplastic left heart syndrome (HLHS) which management remains controversial.
Setting-A tertiary referral centre for pediatric cardiology and cardiac surgery.
Design: A retrospective study of the management and outcome in all cases of HLHS presenting in fetal life between January 1988 and July 2001.
Patients-The diagnosis of HLHS was made in 32 fetuses. One mother had two with HLHS associated pregnancies.
Results: Termination of pregnancy (TOP) was opted for in 16 cases, 4 fetuses died in utero and in 5 parents opted for compassionate care. Seven patients received a palliative reconstructive Norwood procedure, one patient is alive at 17 months. Eight fetuses had extracardiac anomalies, 3 had chromosomal anomalies and 6 had other associated intracardiac anomalies.
Conclusions: Prenatal diagnosis of the HLHS provides opportunities for in depth counselling of the parents before the medical and emotional complexities associated with the neonatal intensive care setting are encountered. Parents faced with the difficult decision of possible termination of pregnancy, compassionate care or the Norwood strategy, tend not to opt for surgery based on the dim perspective of the future quality of life in these patients. The low percentage of intention to treat among patients in European centres differs significantly from reported percentages across the Atlantic. This is most likely based on the socio-geographic and religious differences in the interpretation of the long-term quality of life.

EPIDEMIOLOGY AND PREVENTION MISCELLANEOUS

P1089 Elevated midlife serum cholesterol levels increase the risk of Alzheimer's disease later in life

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Background: Alzheimer's disease (AD), the most common cause of dementia, is a disease of complex origin, the exact pathogenic mechanisms of which remain to be discovered. Recently, evidence for a direct association between serum cholesterol and the development of AD has been documented. Apolipoprotein E (ApoE) e4 allele, involved in cholesterol metabolism, is the most important genetic risk factor for AD. Objective: To study the relative importance and the putative relationship between midlife cholesterol and ApoE polymorphism as risk factors for late-life AD in a longitudinal, population-based study-setting. Methods: Participants were derived from random samples studied in one of the surveys carried out in 1972, 1977, 1982 or 1987. After an average follow-up of 21 years, a total of 1449 (73%) individuals aged 65-79 years participated in the re-examination in 1998. Results: Elevated midlife serum cholesterol was an independent risk factor for AD later in life. Adjusting for ApoE e4 allele and other confounding factors (age, vascular disease, education gender, smoking, and alcohol) did not change the association (OR 2.8, 95%, CI 1.2-6.7). Similarly, ApoE e4 allele was an independent risk factor for AD, even after adjusting for cholesterol and other confounders (OR 2.1, 95% CI 1.1-4.1). The combination of elevated midlife cholesterol and ApoE e4 allele increased the risk of AD in a dose-depended manner; adjusted OR for this combination was 5.9 (2.1-16.3). Conclusions: Elevated midlife cholesterol and ApoE e4 allele constitute independent risk factors for AD. The risk of AD related to elevated serum cholesterol appears to be at least of similar magnitude than the risk related to the most important genetic risk factor ApoE e4 allele. These data emphasize the need for effective primary prevention and early treatment of hypercholesterolemia as potential avenues for reducing the risk of AD.

P1090 Impact of angiotensin-converting enzyme inhibitor administration prior to acute myocardial infarction on hospital and post-hospital morbidity and mortality

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The aim of the study was to determine whether administration of ACE inhibitor therapy prior to acute myocardial infarction (MI) is related to infarct size and subsequent hospital and post-hospital cardiovascular morbidity and mortality.

Methods: Study population consisted of 240 consecutive patients (pts) admitted with a diagnosis of acute MI. Outcome data were compared between groups of patients receiving ACE inhibitor therapy at least three months prior to infarction (ACEI group) and those who were not (non ACEI group).
Results: Sixty-four (27%) were receiving prior ACE inhibitor therapy. There were not significant differences in regard to age, sex, site of infarct, aspirin therapy, frequency of hypertension and diabetes in two groups. Patients in ACEI group experienced smaller MI size, determined by peak creatine kinase elevation ($P<0.01$), and by wall motion score (13.6 ± 1.5 vs 14.3 ± 1.9; $P<0.005$) than pts in non ACEI group. Left ventricular ejection fraction was bigger in ACEI group than in non ACEI group (47.8 ± 7.2 vs $45.4 \pm 8.4\%$; $P<0.05$). In patients receiving ACE inhibitor therapy prior to acute MI, intra-hospital cardiovascular events were less frequent than in those who were not: ventricular fibrillation (8% vs 13%), heart failure (14% vs 21%), re-infarction (6% vs 9%), recurrent angina (14% vs 19%), vascular death (6% vs 10%). There were not significant differences in regard to drug therapy including ACE inhibitor between two groups during the post-discharge 3 months follow up period. After three months the incidence of post-discharge combined morbidity events (re-infarction, CHF, unstable angina, hospitalization, coronary arteriography or myocardial re-vascularization) were slightly higher in non ACEI than in ACEI group (38% vs 30%), as well as the cardiovascular death (5% vs 3%).
Conclusion: Our data showed that patients who experience an acute MI, those receiving prior ACE inhibitor therapy have smaller infarct size, better global left ventricular function and less intra-hospital and post-hospital three months period morbidity and mortality. Thus prior ACE inhibitor therapy have cardioprotective effects in patients with acute myocardial infarction.

P1091 Atrial fibrillation in a cold climate: seasonal variations in morbidity and mortality

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Aims: Seasonal variations in the incidence of myocardial infarction, sudden death and, more recently, heart failure have been described. To date, however, it has not been documented in atrial fibrillation (AF). This study examined whether there is seasonal variation in hospitalisations and deaths due to AF in Scotland.
Methods: We used the linked Scottish Morbidity Record scheme, which provides individualised morbidity and mortality data for the entire Scottish population, to identify all AF-related admissions in Scotland between 1990-1996 and all deaths occurring in those patients who contributed to these admissions between 1990-1997.
Results: During the period 1990-1996, there were a total of 33,582 male and 34,463 female admissions related to AF (either as a principal or secondary diagnosis). This represented an average of 92.3 and 94.7 admissions per day. Significantly more admissions occurred in "peak" winter compared to "low" summer months ($P < 0.01$ for all comparisons). In both men and women, the peak rate of admission occurred in December (9% and 12% more than average) and the lowest admissions rates occurred in June (- 6%) for women and in August (- 3%) for men. The absolute difference in the number of male and female admissions that occurred during these months was 290 and 487, respectively. In both sexes, the greatest variation occurred in those aged > 75 years: peak winter rates being 17-26% higher in those aged 75-84 years and 35-39% higher in those aged 85+ years than average. Seasonal variation in mortality was also seen in these patients with significantly more deaths occurring in "peak" winter versus "low" summer months ($P < 0.001$ for all comparisons). In both men and women, the peak number of deaths occurred in December (22% and 23% higher than average) and the lowest number in August (17% and 14% lower). The absolute difference in the number of male and female deaths occurring during these months was 501 and 723, respectively. Similar trends were observed when these data were analysed according to whether AF was listed as a principal or secondary diagnosis and for short versus longer-term case-fatality rates.
Conclusions: There is substantial seasonal variation in AF-related admissions and deaths in Scotland (particularly in the elderly). A large proportion of this morbidity and mortality is associated with concurrent cardiovascular disease (e.g. stroke and myocardial infarction). Whilst extra vigilance in patients with AF is advisable in winter, further study is required to identify and address the reasons for the marked winter peaks observed.

P1092 Causes of a raised brain natriuretic peptide concentration in an urban population with risk factors for left ventricular dysfunction

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Many studies have concentrated on the use of brain natriuretic (BNP) peptide in diagnosing heart failure (CHF) and left ventricular dysfunction (LVD) in both hospital and community based settings. However, BNP is a marker of increased wall stress and is a non-specific marker of cardiac dysfunction. We aimed to determine the causes of a raised BNP concentration in a sample of 1599 subjects from South Glasgow. 2484 subjects were randomly sampled. All were >45 years and had risk factors for CHF or LVD ie hypertension, diabetes, angina or a previous MI. 1599 attended for a detailed echocardiogram, medical interview, an ECG, a BNP sample and plasma creatinine. Definite systolic dysfunction on echocardiography was defined as a left ventricular ejection fraction (LVEF)<=35% or a wall motion score index (WMI)<=1.4 or at least moderate LVD on subjective coding. Mild LVD was defined as a LVEF<=40% or a WMI<=1.6 or at least mild LVD subjectively. Echocardiograms were analysed for the presence of left ventricular hypertrophy (LVH) and significant valvular disease. An abnormal BNP was defined as being beyond the 95th centile for normals in an age-matched population based study (109.6pg/ml for >70 years and >67pg/ml for those <70).

In this population 333 subjects had a high BNP value. Of those with a high BNP concentration, the following list outlines the causes ranked in descending order and presented as the cumulative number of subjects with the cumulative percentage in parenthesis):the categories are mutually exclusive.

Definite LVD 77 (23.1%), mild LVD 123 (36.9%), MI 171,(51.3%), valve disease 184 (54.3%), a GFR<=60ml/min 234(69.3%), LVH 250 (75.1%), AF 251 (75.4%), GFR between 60-80mls/min 279 (83.8%) and an abnormal ECG 281 (84.4%). No cardiac strutural/functional or renal casue could be identified in the remaining 15.6% of those with an elevated BNP concentration. The remaining subjects were hypertensive or had angina without demonstrable LVH or LVD.

BNP, although higher in concentration, in subjects with CHF and LVD, is a non-specific marker of cardiorenal disease. Where it is used to detect CHF in breathless subjects or to screen for asymptomatic LVD, an elevated value should prompt a cardiological referral.

P1093 Increased mortality rates in patients with coronary artery disease presenting low fasting glucose levels: an 8-year follow-up

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Background: The close relationship between hyperglycemia and increased mortality is well established, but no consistent information is available regarding the association between low glucose levels and cause-specific mortality in patients with coronary artery disease (CAD). We aimed to investigate the relationship between hypoglycemia and all-cause, cardiovascular and cancer mortality in a large population of CAD patients along a mean 8-year follow-up period.

Methods: A total of 14670 patients with documented CAD aged 45-74 years were divided into 6 groups graded across strata of glucose levels upon screening: 1) hypoglycemic (up to 69 mg/dl); 2) low normal (70-79 mg/dl); 3) euglycemic (80-109 mg/dl); 4) patients with impaired fasting glucose (IFG) (110-125 mg/dl); 5) borderline diabetics, comprising patients considered diabetics by the new American Diabetes Association criteria but not by the former World Health Organization criteria (126-139 mg/dl); 6) diabetics (above 140 mg/dl). Mortality rates were separately assessed for each group.

Results: The population comprised 131 patients with hypoglycemia (0.9%), 731 with low normal values (5%), 9308 euglycemic (63.4%), 1577 with IFG (10.7%), 617 borderline diabetics (4.2%) and 2306 diabetics (15.7%). Patients were followed 6.2 to 9.0 years. Crude all-cause mortality was significantly higher in both diabetic (31.8%) and hypoglycemic groups (25.2%) as compared with euglycemic (14.9%; $p<0.0001$), whilst cardiovascular mortality was higher only in diabetics (17.8% vs. 7.9%; $p<0.0001$). The highest prevalence of cancer mortality was documented in the hypoglycemics (6.1% vs. 2.9 in euglycemics; $p<0.02$). Actuarial survival curves showed the lowest mortality rates in euglycemics and in the low normal group, whilst the highest was seen in both diabetics and hypoglycemic patients. Intermediate values were documented for borderline diabetics and patients with IFG. After adjustment for variables, with euglycemic patients as reference group, a significantly higher mortality rate was documented in hypoglycemics when compared with euglycemics ($p<0.0001$). Hypoglycemia was identified as an independent predictor of increased all-cause and cancer mortality with hazard ratios (HR) of 1.84 (95% CI 1.29 - 2.61) and 2.26 (95% CI 1.12-4.57), respectively, but not of increased CAD mortality, with HR 1.30 (95% CI 0.73 - 2.29).

Conclusions: The main findings of this study are the substantially increased all- cause and cancer mortality rates after a mean 8-year follow-up period among patients with CAD presenting low fasting glucose levels.

P1094 Increased circulating levels of natriuretic peptide predict future cardiac events in patients undergoing chronic haemodialysis

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Objective: Cardiovascular events are the major determinant of the prognosis for patients undergoing chronic hemodialysis. The present study was designed to determine whether increased plasma levels of atrial or brain natriuretic peptide (ANP or BNP) can be used to predict future cardiac events in patients undergoing chronic hemodialysis.

Methods: Fifty-three patients undergoing chronic hemodialysis without clinical evidence of cardiac disorders were enrolled in the study. Their blood was sampled for ANP and BNP measurements, and an ultrasound cardiogram and chest X-ray were performed at enrollment. We then followed them up for 11.3±0.2 months, with the endpoint being the occurrence of cardiac events. Cut-off levels of the peptides were calculated using receiver operating characteristics (ROC) curve analysis and the cumulative event-free curves were determined using the Kaplan-Meier method in order to evaluate the predictive values of the cut-off levels.

Results: Cardiac events occurred in 13 patients (CE group). Cardiac events included non-fatal myocardial infarction (1), angina pectoris (1), second grade atrio-ventricular block (1), heart failure (9) and sudden cardiac death (1). Both ANP and BNP levels were higher in patients in the CE group than in patients not presenting with cardiac events (ANP: 118±21 vs 56±5 pg/ml; $p<0.05$, BNP: 769±204 vs 193±25 pg/ml; $p<0.05$, respectively). The length of the hemodialysis period, hemoglobin concentration, cardiothoracic ratios of chest X-rays, findings obtained from ultrasound cardiograms and medication administered were the same in both groups. ROC curve analysis revealed that the cut-off levels, sensitivities and specificities were 58pg/ml, 100.0% and 63.9%, respectively, for ANP and 390 pg/ml, 61.5% and 92.5%, respectively, for BNP. Using the Kaplan-Meier method, the incidence of cardiac events was significantly higher in patients with higher levels of ANP (50.0% vs 0.0%) or BNP (72.7% vs 11.9%) than in those with lower levels of each peptide.

Conclusion: Elevated levels of ANP or BNP indicate an increased risk of the occurrence of cardiac events in patients undergoing chronic hemodialysis. The cut-off levels of these peptides are clinically acceptable and useful for prediction of the occurrence of cardiac events in patients undergonig chronic hemodialysis.

P1095 A population study of left ventricular dysfunction in long-term survivors of myocardial infarction

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More patients are now surviving their myocardial infarction (MI) but do so at the expense of developing heart failure due LV systolic dysfunction (LVD). The aim of this study was to determine the prevalence of LVD by echocardiography in long term surivors of MI within the defined population of North Glasgow, UK. All cases were identified from the MONICA Heart Attack Register for North Glasgow, having sustained a WHO validated first MI between 1985-1992. Each attendee at the study in 1995-6 completed symptom and medication questionnaries and had a full 2D echocardiogram, including a left ventricular ejection fraction (LVEF) by the Biplane Simpson's Rule Method. LVD was taken as a LVEF≤35%. Symptomatic LVD was a LVEF≤35% with breathlessness and/or loop diuretic therapy. Plasma BNP was measured using a direct IRMA method. 924 subjects attended (687 males), at a median period of 7 years post MI (range 2.5-11.5 years). The median age was 62 yrs (34-75). A LVEF could be calculated in 791 (85.6%). The median LVEF was 46.7% (11-76). LVD was identified in 147 subjects (18.6%) and was substantially more prevalent in men (21.6%) than in women (10.3%), $p<0.001$. Symptomatic LVSD was present in 105(71.4%) of those with LVD.

The geometic mean concentration of BNP in those with LVD was significantly higher than in those without (91.20±3.24) vs (29.52±2.82) pg/ml. $p<0.001$. On ROC analysis, the AUC for BNP in detecting LVD was 0.78. A BNP concentration of >=25.85pg/ml diagnosed LVD with a sensitivity of 87.6%, specificity of 42.6% and had a negative precitive value of 94%.

In contrast to previous data based on clinical trial and hospital-based series, this study reports the prevalence of LVD in a population-based study of survivors of MI. The prevalence of LVD is lower than that of the post MI treatment trials and reflects a survival effect. Interestingly the prevalence of LVD was significantly lower in women. BNP also appears to have good diagnostic potential in detecting LVD post MI in this population.

P1096 Trends in proportion of patients in killip class III and IV in myocardial infarction. Variables associated with it and with mortality (1978-1997)

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Background: The development of acute pulmonary edema (Killip class III) or cardiogenic shock (class IV) is associated with a higher mortality in the acute phase of acute myocardial infarction (AMI).
Aims: To analyse the trends in the proportion of patients that develop Killip class III and IV in the acute phase of AMI during a 20-year period (1978-1997), to determine the variables associated with its development and to determine 28-day case-fatality in this subgroup.
Methods: The study is based on a hospital registry of all patients admitted with a first AMI younger than 75 in from 1978 to 1997. Five periods (1978-81, 1982-85, 1986-89, 1990-93 and 1994-97) were defined for analysis. Sociodemographic variables, cardiovascular risk factors, clinical variables, treatments and procedures were recorded. The worst Killip class during hospitalisation and mortality at 28 days were also recorded. Logistic regression was used for statistical analysis.
Results: The registry included 2.590 patients. Mean age was 60 years and 17% were women. Killip class III and IV developed in 13.5% of the patients. There were no changes in this proportion over the five periods. Age, diabetes, previous angina and anterior location of AMI were associated with a higher risk of Killip class III and IV. Case-fatality at 28 days in this subgroup was 51.7%, with a decreasing linear trend over the years ($p<0.001$). Variables associated with a higher case-fatality were age and malignant ventricular arrhythmias. Admission during the periods 1990-93 and 1994-97 was associated with a lower case-fatality (OR=0.37 and 0.28, respectively). The protective effect of these periods disappeared after adjusting for some treatment variables (antiplatelet agents and thrombolysis).
Conclusions: The proportion of patients with AMI that develop Killip class III and IV has remained stable in the last two decades. Although 28-day case-fatality in this patients is high, a decrease has been observed in the last years. This decrease could be explained by the introduction of new treatments (antiplatelet agents and thrombolysis).

P1097 Changes in predictors for cardiovascular mortality between 10, 20, 30 and 40 years follow-up of the Seven Countries Study in Greece

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Background: The Seven Countries Study on cardiovascular diseases has completed in most of the cohorts, approximately, four decades of prospective investigation. In previous analyses the Mediterranean cohorts, and especially the Greeks, showed a markedly decrease in cardiovascular death rates, among the 16 investigated cohorts. Aim of this work is to evaluate, potential, differences in predictors of cardiovascular deaths between 10-20-30 and 40 years follow up.
Methods: From September to October 1961, an international team of specialists examined 529 men from 6 villages. The Corfu cohort was made up of almost all men (95.3%) who were 40-59 years old in the early fall of 1961. Collection of the data on mortality and causes of death was complete for all men for the subsequent 40 years, through visits at villages, ascertaining the fatal events. A survival analysis was performed with CHD mortality as the end-point, while age, blood pressure, total cholesterol, body mass index, smoking, physical activity, skinfold thickness, mid arm circumference, vital capacity and forced expiratory volume, as predictors. Cox proportional hazards models were used in order to assess changes in the investigated parameters.
Results: The death rate varied from 1.5% - 4.3% - 7% and 19.5% in the interim analyses of 10-20-30 and 40 years of follow up, respectively. The predictors for the 10 – years mortality were total cholesterol levels (HR = 1.016, $p < 0.01$) and body mass index (HR = 1.16, $p < 0.07$), for the 20 years CHD mortality were age (HR = 1.14, $p < 0.01$), total cholesterol (HR = 1.013, $p < 0.01$), smoking (HR = 4.51, $p < 0.05$) and vital capacity (HR = 0.943, $p < 0.1$), for the 30 years CHD mortality were age (HR = 1.17, $P < 0.1$), physical inactivity (HR = 3.18, $p < 0.01$), body mass index (HR = 1.064, $P < 0.05$), smoking (HR = 1.6, $p<0.05$), while the predictors for the 40 years mortality were age (Hazard ratio=1.083, $P<0.001$), total serum cholesterol (HR=1.004, $P<0.01$), smoking (HR=1.596, $P<0.05$), and body mass index (HR=1.05, $P<0.05$).
Conclusions: The cluster of the predictors of CHD mortality varies over time, in the investigated cohort. The information raised from this analysis, through a long-term assessment, may be useful in a better understanding of CHD mortality.

P1098 Prevention of CHD: implications of the Framingham study coronary risk appraisal models published in 1991 and 2000

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Background: Recommendations on prevention of CHD and management of hypertension include use of Framingham Study CHD risk appraisal models published in 1991 to identify patients eligible for drug treatment. Updated risk appraisal models published in 2000 incorporate further follow-up and include factors not used in the previously published models.
Methods and Results: We used the 1998 Health Survey for England data for participants aged 35-74 years with complete information on factors required for assessment of CHD risk, after excluding those reporting doctor-diagnosed angina, heart attack or stroke. 10- and 4-year probabilities of developing CHD were estimated using the 1991 equations and 4-year risk was calculated using the 2000 equations. Summary statistics for 4-year CHD risk per 100 persons show that both models produce similar population distributions. While there is substantial agreement between classification of subjects into risk categories based on the two models, within each category based on the 1991 models, individuals were distributed across a wide range of risk categories based on the 2000 models.
Comment: Current guidelines recommend drug therapy for hypertension or hypercholesterolaemia for patients with 10-year risk of 15% and above. As increase in risk accelerates with increasing age, we used a 5% risk of a coronary event in 4 years as being equivalent to a 10-year risk of 15%. Based on the 1991 risk appraisal models, approximately 32% men and 7% women aged 35-74 years in England are at 15% or higher risk of developing heart disease in the next 10 years. Using the 2000 models gives figures of 29% men and 6% women with a 4-year risk of 5% or more. While only 1-2% men and women ineligible for drug therapy under current criteria would be eligible using the 2000 models, 20% men and 43% women currently recommended drug therapy would not be eligible using their 4-year risk based on the updated models. Sensitivity and specificity for the 1991 risk appraisal models would be 97.6% and 90.0% for men and 79.7% and 96.0% for women respectively. A significant number of people meeting drug treatment criteria based on the 1991 models would not meet the equivalent criteria based on the 2000 models. Although thresholds for drug treatment are somewhat arbitrary and depend to a large degree on the resources available, we recommend that these findings are taken into account when current CHD prevention guidelines are updated in accordance with emerging scientific evidence for statin therapy and management of mild hypertension.

P1099 Extent of coronary artery calcifications in HIV-1 positive patients under highly active antiretroviral therapy

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In HIV-1 positive patients under highly active antiretroviral therapy (HAART), especially therapy with protease inhibitors (PI), accelerated arteriosclerosis and an increased incidence of myocardial infarction has been reported. To determine the extent of coronary artery calcifications in HIV-1 infected patients under HAART, we performed electron-beam tomography (EBT). The results were compared to a control group of HIV-1 negative patients.
Methods: EBT was performed in 60 HIV-1 positive patients (50 male, 10 female, mean age 41 years, average infection time 7 years) without known coronary artery disease using a standardized protocol (ECG-triggered, 40 axial slices, slice thickness, 3 mm, no overlap). The degree of coronary calcification was analyzed using the Agatston score. The HIV-1 positive patients were compared to a group of 60 HIV-negative controls (mean age 41 years) matched for age (± 5 years), gender and traditional risk factors (hypertension, cholesterol, diabetes, smoking and family history).
Results: The Agatston score was 37.7 ± 119 in the HIV-1 infected group compared to 19.9 ± 43 in the control group, but this difference did not reach statistical significance ($p = 0.5$, McNemar-Test). PI treated patients ($n = 45$) showed an Agatston score of 47.2 ± 138 compared to 34.6 ± 113 in the group of HIV-1 patients without PI treatment ($p = 0.7$).
Conclusion: In this cross-sectional study, HIV-1 positive patients showed only a tendency towards a more pronounced coronary calcification in comparison to a matched control group. PI treated patients did not differ significantly from patients without PI treatment. However, prospective longitudinal studies are needed to assess the long-term risk of HAART for coronary artery disease.

P1100 Risk factors in African compared to white patients with coronary artery disease (CAD)

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Background Traditional risk factors for CAD have been identified from studies of predominantly white patients in developed countries. Whether these risk factors are equally important in African populations in developing countries is unknown. The aim of this study was to identify and compare risk factors for CAD in African vs. white patients with angiographically documented CAD.
Methods Hospital records of consecutive patients admitted to our hospital over a 2 year period (1998-1999) with 50% or more stenosis of one or more epicardial coronary arteries were analysed. Coronary risk factors including smoking, diabetes, hypertension, obesity, serum total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels were evaluated. Data is reported as median and range, and percentages. Categorical variables were compared by Fisher's exact test or Chi-squared test. Continuous variables were analysed by the Mann-Whitney U-test. A p value < 0.05 was considered significant.
Results There were 207 patients of which 87 (42%) were Africans and 120 (58%) were whites. Age was similar between the 2 groups [59 (24-79) vs. 56 (27-79) years]. There were more females in the African compared to the white group (31% vs. 12%; $p < 0.0229$). Hypertension occurred more commonly in Africans (78% vs. 55%; $p < 0.001$). Serum TC and LDL cholesterol were significantly lower in Africans [4.9 (2.5-8.1) vs. 5.9 (3.3-12)mmolŁ; $p < 0.0006$ and 2.6 (0.9-7.3) vs. 3.8 (1.1-8.1)mmolŁ; $p < 0.0001$ respectively]. No significant differences were observed in the remaining risk factors.
Conclusion Hypertension is more prevalent in Africans with CAD than whites. A female gender appears to confer an additional risk for CAD in African compared to white patients. Baseline LDL cholesterol levels in this group of African patients with documented CAD are exceptionally low and fall into the range recommended by the National Cholesterol Education Program (NCEP) guidelines. These findings may have significant implications for risk factors management in African patients with CAD in developing countries.

P1101 Socioeconomic status and coronary heart disease risk factors: the CARDIO2000 study

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Background: A large number of studies have shown that socio-economic status is related with cardiovascular disease mortality and morbidity among adults, in many developing societies. Aim of this work is to evaluate the relations between social class and various risk factors, in a middle-aged random sample of coronary patients and controls.
Methods: CARDIO2000 project is a population-based study for the primary prevention of CHD. Stratified random sampling from all Greek regions, consisted of 848 hospitalised patients (701 males, 58±10 -147 females, 65±9 years old) for first event of acute coronary syndromes (ACS) and 1078 paired, by sex-age, hospitalised in the same hospitals, controls, without any clinical suspicion of CHD. Social stratification (low, middle and high social class) was based on discriminant analysis of the economical, occupational and educational level of the subjects, according to Tumins' theory.
Results: 491 (58%) of the patients and 561 (52%) of the controls were classified in low class, 187 (22%) patients, 205 (19%) controls in middle class and 167 (20%) patients, 312 (29%) controls in high class ($P<0.01$). The analysis showed higher prevalence of hypertension (28.4% vs. 17.6% vs. 16.5%, $P=0.003$), smoking (36.0% vs. 34.3% vs. 33%, $P<0.01$), job stress (40.0% vs. 25.2% vs. 21%, $P<0.001$), high fat diet (54% vs. 23% vs. 22%, $P<0.01$) and high alcohol consumption (37% vs. 22% vs. 21%, $P<0.05$), between the social classes. The multivariate model showed that subjects in middle class have 45% increased coronary risk compared to subjects in high class (OR=1.45, $P=0.003$), while subjects in low class have 42% higher coronary risk (OR=1.42, $P=0.001$), after taking into account the effect of several potential confounders.
Conclusions: It seems that subjects in low-middle class need more attention from the preventive strategies, since they are more vulnerable in developing ACS compared to the others. A potential explanation is due to the adoption of unhealthy lifestyle habits and the increased prevalence of hypertension in low-moderate social class, but further investigation is needed in order to confirm or refute our findings.

P1102 Education level: association with cardiovascular risk factors and all-cause mortality

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The association between low educational level (EL) and poorer health has been documented in previous reports. The aim of our study was to specify the relationship, first between EL and cardiovascular risk factors, and secondly between EL and overall mortality in a population based study.
In 1982-1984, we surveyed 3690 people -3210 men (87.0%) and 480 women (13.0%)- working in 4 factories of the area of Lyon, France (response rate 90.1% of the target population). Their mean age was 41.4±9.33(DS) and 39.6±9.2(DS) years, respectively. EL was categorized in 4 groups: less than 6 years (primary school)(N=812), up to 10 years (secondary school)(N=1726), up to 15 years ("baccalauréat")(N=683), university (N=466). For each subject, we got data about smoking, alcohol consumption and other dietary habits, physical activity, and current medications. Then, weight, height, blood pressure and heart rate were measured, and a blood sample was taken for assessment of cholesterol, triglycerides, blood glucose, and renal and liver tests.
Using ANOVA statistics, we found that lower EL was significantly associated with higher frequency and/or higher level of cardiovascular risk factors, especially cigarette smoking, excessive alcohol consumption, overweight (Body Mass Index), and lack of physical activity in leisure time. It was also significantly associated with faster heart rate, higher diastolic and systolic blood pressure, hypercholesterolaemia (total and LDL-cholesterol), hyperglycemia. In women, we found an association between lower EL and the simultaneous use of oral contraception and cigarettes. The subjects with lower EL were also older but all the relations remained statistically significant after adjusting for this main confounder in an analysis of covariance. Then, using Kaplan-Meier curves, we showed that there is an inverse relationship between EL and all-cause mortality, with an average follow-up duration of 15 years. In men, the mortality was 15.1% in the primary EL group and 4.2% in the university group ($p<0,00001$).
Our results emphasize the inverse relationship between EL and cardiovascular risk factors, and mortality, which was partly explained by less favourable health habits. These results have strong implications for public health education. Prevention programs must be appropriate to the targeted audience. In addition, they must address not only specific cardiovascular risk factors, but also more general risk behaviors, keeping in mind that those are related to social conditions.

P1103 Impaired cognitive function as a risk factor of in-hospital mortality in older patients with heart failure

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Heart failure (HF) and impaired cognitive function are frequent causes of hospitalization in elderly patients. Independently, both clinical syndromes are associated with increased mortality. The aim of the study was to evaluate the influence of impaired cognitive function on in-hospital mortality in old patients with HF. A modified Mini-Mental State Exam (MMMSE) was performed in 597 consecutive patients (65 - 102 years old; 355 female) with heart failure. All patients were stratified into low (6.3±1.2 points), medium (19.7±4.7 points) or high (29.1±2.1 points) tertile group according to MMMSE results. Total in-hospital mortality was 52.0% in the lowest, 34.2% in the medium and 15.1% in the highest tertile (Pearson Chi-square $p < 0.0001$ for trend). The comparison of in-hospital mortality between tertiles of MMMSE was done with the use of logistic regression adjusted to age, sex, and the presence of diabetes mellitus, renal failure and anemia. Comparison of in-hospital mortality between patients from the lowest tertile of MMSE with the highest one revealed that odds ratio was 5.93 (95% CI: 3.58 - 9.80; $p < 0.0001$) whereas it was 2.67 (95% CI: 1.60 - 4.67; $p = 0.0002$) for patients from the medium tertile. The obtained results show that the worse cognitive function is, the worse in-hospital prognosis can be observed in older patients with HF. Moreover, it also suggests that impaired cognitive function may be an independent risk factor for mortality in elderly HF patients.

P1104 Post traumatic stress disorder is the most important determinat of adherence with aspirin treatment 6 months after an acute myocaridal infarction

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Nonadherence to (no compliance with) medications following a myocardial infarction has been reported to be a major cause of post-myocardial infarction (MI) morbidity and mortality. We have previously introduced a novel hypothesis, linking symptoms of posttraumatic stress disorder (PTSD) to nonadherence in these patients. According to this hypothesis, patients who are traumatized by the MI may not take their medications because these serve as a painful reminder of the traumatic event. To explore this hypothesis further, we examined this association in a cohort of post-MI patients in an outpatient setting.

Patients and Methods: 100 patients were approached 6 months following an acute MI and 82 gave informed consent and enrolled. In a separate study, we evaluated 3 different methods of assessment of adherence to aspirin by platelet function and found that TxA2 production is the most reliable method. This was also reported by others. Patients where asked to answer a validated PTSD questioner (impact of event scale, 15 brief questions) and validated questioner examining broad psychopathology constructs (SCL-90-R).

Results: Above-threshold PTSD scores were associated with nonadherence (p=0.02). Other baseline variables (sex, age, employment, family status), background diseases (diabetes, hypertension, functional class) as well as psychopathological characteristics where not associated with nonadherence. Patient self-report was also did not reliably predict adherence in the present study.

Conclusion: PTSD symptoms are significantly associated with nonadherence to medications following an acute MI. These symptoms can easily be assessed in a clinical setting. If indeed medications serve as a painful reminder of the MI to patients who are traumatized by it, then trauma specific interventions hold the promise to improve adherence and hence outcome in these patients. Such treatments where previously reported by us to improve adherence in another disease process.

P1105 Stress, multiple roles and coronary disease in women. The Stockholm female coronary risk study

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Objective: Once women get coronary disease, their prognosis is poorer and they are less likely than men to get rehabilitated, even after control for age and comorbidity. Possible reasons for this gender difference include the chronic and daily stresses of work and family roles, which may add to the burden of physiological risk factors in younger women.

Background and methods: In the Stockholm Female Coronary Risk Study,women patients who reported emotional stress from their dyadic relationship, as assessed by the Stockholm Martial Stress Scale, were more vulnerable than women who reported work stress, by the Karasek model.We further hypothesized that women who, at the same time, experienced martial and work stress may be at even greater risk of worsening coronary disease and that depressive symptoms may mediate the effects of such stress.The age and multivariated adjusted hazard ratios for the five year risk of a recurrent cardiac event in women patients, was 2.9 for marital stress (95% CI 1.3-6.5) and 1.6 for work stress (95% CI 0.8-3.3). About one third of women patients experienced marital and work stress concomtantly. Their hazard ratio for a recurrent event was 5.7 (95% CI 1.3-24.3).

Results: Women patients reporting both types of stress had an average of 5.0 (±0.6) depressive symptoms, whereas patients without any stress had 1.5 (±0.6) symptoms.

Conclusion: Patients with both marital ad work stress were at highest risk of recurrant events. Effects of multiple stress expereinces were synergetic and possibly mediated by depressive symptoms.

P1106 Hereditary haemochromatosis gene mutations, prevalence and severity of coronary artery disease

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A mutation in a nonclassic MHC class I gene (HFE gene), resulting in a cysteine-to-tyrosine substitution at amino acid 282 (Cys282Tyr) has been shown to be the major cause of hereditary haemochromatosis. Heterozygotes are common in the European population (about 10%) and have slight iron overload. Individuals carrying the mutation were reported to have an increased risk of myocardial infarction and cerebrovascular death. But there are also conflicting results. We investigated the influence of the Cys282Tyr mutation on prevalence and severity of coronary artery disease (CAD) in a large angiographically controlled population.

Methods: We genotyped 1279 patients (pts) who underwent coronary angiography at our institution. Pts with a >50% stenosis were diagnosed to have CAD. The Gensini score, an established score to describe severity and functional significance of CAD, was used. Genomic DNA was extracted from blood leukocytes and standard PCR was performed to detect G-to-A transition, resulting in the Cys282Tyr mutation in the HFE gene.

Results: 116 pts (9.1%) carried the heterozygous mutation, 1 patient was homozygous. The estimated mutant allele frequency was 0.048. The genotype distribution in our population was not statistically different from expected Hardy-Weinberg-equilibrium.

In a multivariate analysis conventional risk factors but not the Cys282Tyr mutation were associated with the prevalence of CAD (table). Incidence of previous myocardial infarction was also not influenced by the mutation. In established CAD, the Cys282Tyr mutation was not associated with an extended disease.

	Odds ratio	95% CI	p*
Cys282Tyr mutation	1.46	(0.84 - 2.55)	0.17
male	3.21	(2.31 - 4.47)	<0.0001
diabetes	2.27	(1.54 - 3.33)	<0.0001
hypertension	1.02	(0.75 - 1.38)	0.90
smoking [10 py]	3.23	(2.29 - 4.56)	<0.0001
age [10 years]	2.02	(1.72 - 2.37)	<0.0001
LDL cholesterol [0.5 mmol/l]	1.10	(1.03 - 1.18)	0.002

*logistic regression analysis.

Conclusions: Our findings in over 1000 pts do not support an association of hereditary haemochromatosis gene and prevalence or severity of CAD.

P1107 G20210A prothrombin gene polymorphism and coronary ischaemic syndromes: an up-dated meta-analysis of 10620 subjects

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Background: Two overviews have reported the lack of a significant association between the G20210A prothrombin gene polymorphism and ischemic heart disease (IHD). However, an up-to-date, phenotype-specific analysis is currently not available.

Aim: We conducted a meta-analysis of 17 studies published in extenso (within January 2002) on the association between the G20210A prothrombin variant and IHD (globally including 4293 patients and 6327 controls). Our specific aim was to investigate the possible link between the G20210A variant and predefined phenotypic markers (age, clinical presentation, angiographic extent of coronary disease, traditional cardiovascular risk factors).

Methods: The following data were extracted from each study: sample-size, inclusion criteria, geographical location, clinical presentation, and age. Cardiovascular risk factors (hypertension, smoking, dislipidemia, diabetes), angiographic extent of disease, and heterogeneity among studies were systematically sought for. The analyses were performed according to Mantel-Haenszel.

Results: Overall, the 20210 A allele was associated with an odds ratio (OR) for unspecified IHD of 1.19 (95%CI 0.96-1.59). Similar findings were seen for acute coronary syndromes (unstable angina and myocardial infarction) or myocardial infarction (MI) without age-limits (OR=1.22, 95%CI 0.94-1.66, n=8502, and OR=1.21, 95%CI 0.93-1.66, n=8830, respectively). The OR for MI increased to 1.77 (95%CI 1.16-3.42) in the 1931 subjects <55 years of age and to 2.30 (95%CI 1.27-4.59) in the 1359 subjects <45 years. Patients with 0- or 1-vessel disease at angiography showed a greater prevalence of the A allele compared to those with multivessel disease (relative risk 2.0, 95%CI 1.2-3.1, n=2376). The published data were insufficient to allow pooled evaluations of the interactions between G20210A and traditional cardiovascular risk factors.

Conclusions: These data indicate that the G20210A prothrombin gene polymorphism represents a modest but significant risk factor for MI below the age of 55 years. Moreover, it may favour the expression of IHD among patients who have limited extent of coronary atherosclerosis at angiography.

P1108 Newly detected gene variation of the cholesteryl ester tranfer protein (CETP) strongly predicts prognosis and response to statin therapy

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Introduction: Cholesteryl ester transfer protein (CETP) plays a key role in the HDL metabolism. Variations in the CETP gene determine CETP activities as well as HDL-cholesterol concentrations and might influence prognosis and response to statin therapy.
Methods: In 1303 CAD patients we tested the hypothesis that the CETP/C-629A, I405V, and TaqIB variant of the CETP gene affects CETP activity, HDL-cholesterol concentration and prognosis of CAD. TaqIB variant and CETP/C-629A genotype were in nearly complete association.
Results: Patients carrying the -629A allele had significantly lower CETP activities and higher HDL concentrations. We observed a highly significant dose-dependent association between this genetic marker and future mortality from cardiovascular causes (n=120) after a median follow-up of 4.1 years. Mortality decreased from 10.4% in homozygous C allele carriers to 4.7% in heterzygous to 4.0% in homozygous A allele carriers (P<0.0001). This association was independent of potential confounders such as A allele carriers reveal a 0.35 (95% CI 0.21 to 0.67, P<0.0001) decrease in risk in a fully adjusted model (see legend Table 1). In addition, this association was only present in patients without statin therapy. The benefit of statin therapy was restricted to patients carrying the C-allele of the C-629A genotype (P for interaction 0.02). Patients carrying the CETP/405V allele tended to have higher HDL concentrations and lower mortality rate but this association did not achieve independent significance.

CETP/C-629A	CC	CA	AA	P-univ.	P-multiv.
all pts	10.4	4.7	4.0	<0.0001	0.002
without statins	13.0	4.6	3.0	<0.0001	0.001
with statins	5.8	5.0	6.0	0.9	0.5

P values given are P for trend; P multivariate controlled for age, sex, classical risk factors, clinical and therapeutic features such as unstable angina, extent of vessel disease, history of MI, interventional strategies, betablocker and statin therapy (if appropriate) and ejection fraction.

Conclusion: We observed a significant relation between CETP/-629 A allele carriers, decreased risk of future mortality, increased HDL-concentrations, and decreased CETP activity. This common mutation appears to predict whether or not patients with CAD will experience a survival benefit from statin therapy.

P1109 Pharmacogenetics in thrombolytic therapy. Role of Factor XIII Val34Leu polymorphism

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The Val34Leu polymorphism of Factor XIII (FXIII) A-subunit gene is associate with increased FXIII fibrin cross-linking activity. However, contradictory data is available about its role in thrombotic disease. Recently we have observed a higher prevalence of the Leu34 allele in premature acute myocardial infarction. Remarkably, the Leu/Leu genotype increases the risk (odds ratio:3.54; 95% CI:1.22-10.22) after multivariate analysis (p:0.019). Thrombolytic therapy is used to open quickly the acute coronary occlusion. Unfortunately one half of treated patients do not achieve optimal tissue perfusion. We hypothesise that clots might show different sensitivity to thrombolytic therapy, and this could be influenced by the FXIII Val34Leu polymorphism.
Methods: Genetic analyses were performed on 180 consecutive young patients with myocardial infarction before 45 years from our cardiology outpatients clinic. We analysed the effects of thrombolytic therapy. Thrombolytic agents were given in a standard dose. The ineligibility criteria for reperfusion therapy were recorded. Non-invasive assessment of the efficacy of coronary thrombolysis was evaluated by serial electrocardiograms and creatine kinase time-activity curves. Declination of ST segment elevation upper than 50% in 90 minutes and an early peak of creatine kinase (under 12 hours) were considered as reperfusion criteria.
Results: Genetic frequences were 108 (60.0%) Val/Val, 59 (32.8%) Val/Leu, 13 (7.2%) Leu/Leu. Seventy-two patients were treated by thrombolytic therapy. Three thrombolytic agents were used: streptokinase (n=4), APSAC (n=9), and tissue plasminogen activator (n=59 patients). Acute coronary angioplasty was performed in 11 patients (Val/Val: n=5, Val/Leu: n=5 and Leu/Leu: n=1). Efficacious thrombolysis was observed in 44/50 patients with Val/Val genotype, but only 13/22 patients carrying the Leu34 allele (Leu/Val or Leu/Leu). The efficacy of thrombolytic therapy was significantly upper in patients with Val34 allele (p: 0.005; odds ratio 5.08; confidence interval 1.32-20.22). There were no differences in the success between the different thrombolytic drugs. Interestingly, all the acute angioplasties were successful and these patients showed a good initial evolution (1st month).
Conclusions: We report the first clinical evidence suggesting that the Leu34 allele could reduce the efficacy of the thrombolytic therapy.

HYPERTENSION, OTHER RISK FACTORS AND CARDIOVASCULAR DISEASE

P1110 Doppler echocardiographic coronary flow reserve: a marker of global cardiovascular risk in uncomplicated arterial hypertension

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In order to analyse the impact of global cardiovascular risk on coronary microcirculation, our aim was to assess the impact of coronary risk factors (RF) on coronary flow reserve (CFR) in uncomplicated arterial hypertension.
Methods: 64 newly diagnosed hypertensives (mean age = 50 years, M/F = 49/15), free of cardiac drugs and coronary artery disease (clinical history + effort ECG) underwent: anamnesis to identify standard RF; determination of body mass index (BMI), clinic BP and heart rate (HR); M-mode echo and second harmonic Doppler of distal left anterior descendent coronary artery, at baseline and after dypiridamole vasodilation (0.56 mg/Kg IV over 4') to estimate CFR (hyperemic to baseline diastolic flow velocity ratio).
Results: Blood pressure (BP) was 148/101 mm Hg and BMI 27.8 g/m^2, with overweight prevalence (BMI > 27 g/m^2) of 56%. The metabolic profile showed: glycemia = 97.5±12 mg/dl (hyperglycemia prevalence [>110 mg/dl] = 15.6%), total cholesterol = 222±45 mg/dl (hypercholesterolemia [>200 mg/dl] = 59.4%), triglycerides = 151±71 mg/dl (hypertrygliceridemia [>180 mg/dl], = 27%). Left ventricular hypertrophy (LVH = left ventricular mass index [LVMI] >50 g/m powered to 2.7) was found in 41% of hypertensives. In the overall population we observed negative association of CFR with HR (r=-0.33, p<0.005), diastolic BP (r=-0.40, p<0.001), glycemia (r=-0.28, p<0.02), total cholesterol (r=-0.41, p<0.001) and LVMI (r=-0.28, p<0.02). In a multivariate model, BMI (beta coefficient =0.42, p<0.0005), cigarette smoking (beta=-0.33, p<0.001), LVMI (beta=-0.30, p<0.005) and total cholesterol (beta=-0.26, p<0.01) were independent predictors of CFR (cumulative R square = 0.45, S.E.=0.38, p<0.00001) while the partial relation coefficients of sex, age, diastolic BP, glycemia and triglycerides were not significant. By analyzing the cumulative impact of RF (hypertension, smoke, cholesterol, glycemia), CFR was 2.20 in patients with 1 RF (only hypertension), 2.17 with 2 RF, 1.71 with 3 RF, 1.55 with 4 RF (p<0.0005). The addition of LVH to standard RF reduced further CFR only in the higher risk groups (from 1.71 to 1.60 in the group with 3 RF, from 1.55 to 1.38 in the group with 4 CRF, both p<0.01).
Conclusions: Except for overweight which is associated to a greater CFR, the concept of global risk may be applied also to the coronary microvessels. CFR is an early marker of coronary involvement in arterial hypertension, before the development of overt coronary artery disease.

P1111 Birth anthropometry and later blood pressure

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The Barker's hypothesis suggested a link between low birth weight (BW) and risk of adulthood cardiovascular disease; this association may be the result of fetal adaptation to an adverse intrauterine environment. A number of studies suggest that body mass index (BMI) and blood pressure (BP) values are rising among sedentary school children; these changes may have future health implications for cardiovascular disease.
The objective of this study was to examine the effect of birth anthropometry (head circumference,BW,birth lenght)on health status development in children. The BP of 1540 school children (F 710, M 830; 11-12 years) was recorded at a screening medical examination; the parents were asked to fill in a questionnaire that included demographic data, family history, parent's weight and height, children's perinatal measurements and his or her involvement in physical activity (PA).
BW and children's BP at baseline examination are not correlated (p 0.1); BW is also unrelated to children's (p 0.1) and parent's (p 0.1) BMI; we observed a positive correlation between parental and children's BMI (paternal BMI p <0.01 r 0,2; maternal BMI p<0.001 r 0.4) and a negative correlation between PA and SBP (p<0.001 r0,3), DBP (p<0.001 r0,4), children's BMI (p<0.001 r0,4). Parent's smoking was additive predictor in children of lower physical activity (p <0.01); furthermore children's body mass index (p<0.001), BP values (p<0.001) and incidence of asthma (p<0.02) were significantly greater if parents smoked. Step-wise multiple regression analysis with BP values as dependent variable and children's, birth's and parent's antropometric measurements, familial history of disease and PA as indipendent variables showed that PA and children's BMI were the variables carrying the greatest weight on BP values; furthemore step-wise multiple regression analysis with children's BMI as dependent variable and birth's and parent's antropometric measurements, familial history of disease and PA as indipendent variables showed that PA was the variables carrying the greatest weight on children's BMI.
These data suggest that lifestyle, rather birth weight, is the early life factor most importantly related to subsequent BP and BMI in childhood.

P1112 A deletion-insertion polymorphism in the alpha-2B adrenoceptor gene modifies the response to antihypertensive drugs: a pharmacogenetic study

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Background: While specific antihypertensive agents are recommended to start therapy, their blood pressure lowering effect in a given patient remains unpredictable. To provide information for personalized choice of antihypertensive agents, we carried out a pharmacogenetic population study to investigate, how a functional polymorphism in the alpha-2B-adrenoceptor (AR) gene modifies effects of common antihypertensive agents.
Methods: The subjects were the participants in the KIHD study, a population study of genetic and non-genetic risk factors of cardiovascular and related diseases. DNA samples were available of over 1500 men aged 42-60 years at baseline. Of these, 834 men participated in a 11-year follow-up study in 1998-200, at the age of 53-71 years. The antihypertensive effect of each drug category was estimated by comparison with other antihypertensive drugs.
Results: Beta-blockers reduced the mean arterial pressure by 6 mmHg in deletion carriers and none in non-carriers (p=0.009, n=834), whereas diuretics and calcium-channel blockers were antihypertensive only among the wild type (insertion homozygotes). Among 498 normotensive men, deletion homozygosity increased the 11-year incidence of hypertension 3.2-fold (95% confidence interval 1.8 to 5.8, p<0.001).
Conclusion: Our findings indicate that in men with deletion in the alpha-2B-AR gene there is an increased risk of becoming hypertensive and enhanced antihypertensive efficacy of beta-blockers, whereas the effect of diuretics and calcium-channel blockers may be attenuated. Our findings show that the I/D polymorphism of the alpha-2B-AR gene modifies the blood pressure lowering efficacy of the most commonly used antihypertensive drug types. Genetic tests, such as DNA chips, can be developed for the use in the personalized medicine for the genetic subdiagnosis of hypertension and for targeting drug treatments both in drug research and development as well as in the clinical practice. These tests could bring, besides improvement in the care of hypertensives, sizeable savings both in the drug development and in the health care.

P1113 Pulse pressure as a predictor for stroke mortality, in elderly individuals: forty years follow-up of the Corfu cohort; Seven Countries study

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Background: Epidemiological evidence indicates that hypertension predisposes to stroke. Although pulse pressure reflects aortic distensibility, the data on stroke mortality are limited in literature. This analysis aims at describing the role of increased pulse pressure on the stroke mortality, based on 40-years (1961-2001) prospective evaluation of the Corfu cohort, from the Seven Countries Study.
Methods: The population studied in this analysis consisted of rural men enrolled at 1961 (n=529, 49.7±5.7 years old) in Corfu. Among several factors systolic, diastolic blood pressure levels and their difference (pulse pressure) was evaluated with stroke mortality as the end-point. Cox proportional hazards models were applied in order to evaluate the investigated parameters. A major limitation of the study was our inability to segregate thrombotic from hemorrhagic strokes.
Results: Among 529 cardiovascular disease-free men at entry, 65 (12.3%) died because of cerebrovascular disease. The cumulative survival at the end of the follow-up was 76%. Mean age at death for stroke was 75 ± 9 years old. At baseline, Age (HR = 1.125, p < 0.001), systolic blood pressure (HR = 1.021, p < 0.001), physical activity (HR = 0.583, p < 0.05), and total serum cholesterol (HR = 0.990, p < 0.01) showed a statistically significant association with cerebrovascular disease incidence. The difference between systolic and diastolic blood pressure (pulse pressure) was significantly associated with stroke mortality (HR = 1.025, p < 0.001), after adjusting for age, physical activity, cholesterol levels, smoking habits and body mass index.
Conclusions: In these elderly men 40-years incidence of cerebrovascular disease seems to be strongly associated with pulse pressure levels, at baseline. The baseline pulse pressure is more significant predictor for stroke mortality than systolic blood pressure, as it represents the loss of aortic distensibility due to atherosclerosis.

P1114 Prevalence of primary aldosteronism among hypertensive patients

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Aim: There is increasing evidence that primary aldosteronism (PA) may be common in patients defined as "essential" hypertensive. Aim of this study was to evaluate the incidence of primary aldosteronism in a primary-care hypertensive population.
Methods: Five hundred and five consecutive unselected hypertensive patients (298 female and 207 male, 156 untreated and 399 treated, age 25-75 yr) attending to our hypertensive unit, had ambulatory measurements for plasma aldosterone and plasma renin activity (PRA); electrolyte measurements were obtained simultaneously. Subjects with renal insufficiency and those treated with glucocorticoids or spironolactone were excludes. Antiypertensive medication was stopped for 7 days in the treated patients before the blood sample collecting for aldosterone and PRA evaluation. The aldosterone to PRA ratio was used as an initial screening test to identify potential patients with PA. The patients with an elevated ratio (> 25) were admitted for the salt loading suppression test. Adrenal computed tomographic scansion was performed in biochemically confirmed cases.
Results: Seventy-one of the 505 hypertensive patients had a positive aldosterone/renin ratio; in 70 of them confirmatory studies were carried out. Using an aldosterone concentration above 7.5 ng/dl after saline infusion as the diagnostic cut-off, 35 patients had biochemically confirmed primary aldosteronism. Among these individuals, only four were hypokaliemic; an adrenal mass was detected in three patients.
Conclusion: primary aldosteronism has been traditionally regarded as a rare cause of hypertension. However the availability of the aldosterone-renin ratio as a screening test and its application to a wider population of hypertensives has resulted in a marked increase detection rate. Our data suggest that primary aldosteronism occurs in at least 6.9% of the adult hypertensive population.

P1115 Awareness of blood pressure decreased dramatically during the last decade in Poland

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The aim of our study was to evaluate changes in awareness of blood pressure (BP) during transition into market economy in Poland. Thus, in 1994 (NATPOL I, n=2080), 1997 (NATPOL II, n=1664) and 2001/2002 (NATPOL III, n=3052), we repeated the cross-sectional surveys based on questionnaire interviews on representative samples of adults in Poland, aged 18 years and over. The subjects were selected from Polish population by stratified and cluster random sampling with quotas. They were asked, if they were aware of blood pressure. The results were analysed according to age, sex, education level, income and place of living. Overall, awareness of blood pressure declined ($p<0.001$) from 71% in 1994 to 65.5% in 1997, and to 59% in 2001/2002. The data according to sex, level of education and place of living are shown in the table.

	1994	1997	2001/2002
women	77	71	64
men	65	60	54
primary or post-primary education	68	59	51
secondary or higher education	75	74	68
large cities (>200 000)	72	73	67
small cities	77	66	62
villages	65	61	52

Decline of awareness of BP was most significant in small cities and villages as well as among less educated people representing lower social status. Low awareness of blood pressure in Poland emphasizes the need for urgent preventive measures.

P1116 Homocysteine, fibrinogen and C-reactive protein levels by hypertension status, in cardiovascular disease free subjects: the ATTICA study

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Aims: The aim of this study is to evaluate the levels of homocysteine, fibrinogen and C-reactive protein, by hypertension status, in a random sample of cardiovascular disease-free subjects.
Methods: The ATTICA study is a population -based prospective cohort designed to enrol 3073 men and women from the greater area of Athens. A random algorithm was developed and stratified, by sex- age; sampling was performed, during 2001. In this work we analysed data from 654 men (18-87 years old) and 826 women (18-89 years old). Hypertension was defined as SBP > 140 mmHg or/and DBP > 90 mmHg, or under special treatment. Among several investigated factors serum homocysteine, fast plasma fibrinogen concentration and C-reactive protein levels were evaluated, through multivariate analysis.
Results: A hundred and twenty-six (19%) of males and 132 (16%) of female subjects were defined as hypertensives. The statistical analysis showed that fibrinogen levels were significantly higher in hypertensives compared to the rest of them (346±75 vs. 317±83, $p < 0.001$). Similar results were observed in C-reactive protein levels (hypertensives: 3.07±1.5 vs. normotensive 2.18±1.9 mg/dl, $p < 0.01$), while no significant association was found between hypertension and homocysteine levels (14.3±4.2 vs. 13.2±6.1, $p = 0.246$). The results become more consistent when we evaluated continuous measurements of SBP and DBP in relation to the investigated factors. The previous findings, were, also, confirmed by the multivariate analysis that took into account the effect of age, sex, smoking status and physical activity status of the subjects.
Conclusions: Results from this population-based survey indicate that fibrinogen and C-reactive protein are strongly associated with the presence of hypertension, while homocysteine showed borderline trend. This may partially explain the mechanism by which elevated levels of these emerging risk factors may affect coronary risk. However, the prospective evaluation of the present study may confirm or refute our findings, in relation to cardiovascular disease, at population level.

P1117 Pulse pressure as an indicator of future development of isolated systolic hypertension in previously normotensive individuals

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Background: It is well known that there is a strong continuous, graded, consistent and etiologically significant relation between systolic blood pressure (SBP) and cardiac risk, while pulse pressure (PP) is considered as an independent risk factor for cardiovascular and renal disease. This prospective study was designed in order to examine the possible role of PP in the future development of isolated systolic hypertension (ISH) in previously normotensive subjects.
Methods: Three hundred and fifty normotensive volunteers (150M, 200F) mean age (MA) 60±8 yrs and body mass index (BMI) 23±1.8 Kg/m^2 were studied. Systolic, diastolic blood pressure (SBP, DBP) and PP levels were determined and followed-up for a 5 year time period, in the whole study population.
Results: During the follow-up period, 50 out of 350 (20M, 30F, 14.3%) individuals developed ISH (Group A), while 300 out of 350 (130M, 170F, 85.7%) remained normotensive (Group B). The characteristics of both groups in the start of this prospective study are shown in the table.It is obvious that the PP levels are significantly increased in group A.

	Group A	Group B	p
MA (years)	59±6	58±8	NS
BMI (Kg/m^2)	23±1.6	22.8±1.7	NS
SBP (mmHg)	136±3	134±4	NS
DBP (mmHg)	80±6	82±5	NS
PP (mmHg)	55±3	52±2	<.001

Conclusion: The results of our study suggest that PP may consist an individual indicator for the future development of ISH in previously normotensive subjects without any other predisposing risk factor.

EXPERIMENTAL HEART FAILURE

P1118 "In vivo" antihypertrophic effect of the sodium/proton exchange inhibitor cariporide

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"In vitro" studies showed that the sodium/proton exchange inhibitor cariporide markedly reduces the growth-promoting effect of rhythmic mechanical stretch in cultured mouse cardiomyocytes. Our goal was was to establish whether this compound may exert antihypertrophic influences "in vivo".
Pressure overload was induced by thoracic aortic banding (Bd) in 3 month-old mice (n=16). Animals were treated with oral cariporide, 1 mg.kg-1 (Bd-Car, n=8), or vehicle (Bd-Veh, n=8). Concurrent groups of sham (Sh)-operated mice were studied (Sh-Car, n=8; Sh-Veh, n=8). Treatments were started 3 days before surgery and continued until two weeks post-surgery, after which i) blood pressure was measured via a right carotid catheter implanted under light anesthesia; ii) the mouse was euthanized, the heart removed and the left ventricle isolated and weighed, the absolute figure (LVW, mg) being normalized to body weight (BW, g); iii) LV cardiomyocyte cross-sectional area (CCSA) and the extent of LV fibrosis were assessed by computer-assisted histomorphometry.
Systolic blood pressure (SBP) was significanly higher in Bd-Veh compared to Sh-Veh mice (145±4 vs 112±3 mmHg, $p<0.01$), and was not affected by cariporide treatment (143±2 and 114±5 mmHg in Bd-Car and Sh-Car mice, respectively, p=ns compared to each Veh counterpart). As expected, Bd-Veh mice had markedly higher LVW/BW ratios than Sh-Veh mice (4.5±0.2 vs 2.9 mg/g, $p<0.01$, a 55% increase); cariporide treatment had no effects on LV weight in Sh-Car mice (3.0±0.1 mg/g, p=ns vs Sh-Veh) but dramatically attenuated its increase in Bd-Car mice (3.4±0.1, $p<0.01$ vs Bd-Veh, a 70% atternuation). Histomorphometry (data not shown) provided results largely paralleling the autoptic results, with an increase in CCSA of about 50% in Bd-Veh compared to Sh-Veh mice and with an approx 70% inhibition of such increase by cariporide treatment. In contrast, findings were different concerning fibrosis: as expected, banded animals had markedly fibrotic left ventricles, with almost twice as much collagen stained in Bd-Veh compared to Sh-Veh mice, but cariporide treatment failed under this regard to display any protective effect.
We conclude that the sodium/proton exchange inhibitor cariporide i) markedly attenuates the development of LV hypertrophy "in vivo", with significant implications for understanding the mechanisms and possibly improving the treatment of this prognostically unfavourable condition, and ii) selectively interferes with growth processes in the myocyte but not in the connective tissue component of the left ventricle.

P1119 p38 MAP kinase phosphorylation and apoptosis in pacing-induced heart failure

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In human hypertrophied and in human chronically ischemic, failing myocardium, the phosphorylation of p38 mitogen activated protein kinase (MAPK) is increased. In experimental studies of ischemia/reperfusion, increased p38 MAPK phosphorylation is associated with increased myocyte apoptosis.
We now tested whether or not p38 MAPK is also activated in pacing-induced heart failure (HF) in rabbits, which is neither associated with significant myocardial ischemia nor left ventricular (LV) hypertrophy.
In seven chronically instrumented rabbits, HF was induced by rapid LV pacing (400 bpm). After 3 weeks of pacing, the rabbits displayed clinical signs of HF. Echocardiography revealed an increase in LV end-diastolic diameter from 14±1 to 17±1 mm and a reduced LV shortening fraction from 37±2 to 12±2% (Mean±SEM, both $p<0.05$). Eight sham-operated rabbits served as controls. Total p38 MAPK did not differ between HF rabbits (239,050±25,951 AU, densitometry) and controls (229,831±21,049 AU). However, p38 MAPK phosphorylation was significantly increased in HF rabbits (76±6% of total p38MAPK) compared to controls (28±6%, $p<0.05$). The number of TUNEL-positive cardiomyocytes, as a measure of the extent of apoptosis, was also significantly increased in HF rabbits (0.025±0.006%) compared to controls (0.003±0.001%, $p<0.05$). Overall, p38 MAPK phosphorylation correlated to the extent of apoptosis ($r=0.60$).
Conclusion: In this HF model with reduced LV systolic function, p38 MAPK phosphorylation and the extent of apoptosis are increased. Further studies will have to define whether or not chronic blockade of p38 MAPK activity can interfere with apoptosis and thereby attenuate the progression of HF.

P1120 AT2-receptor activation regulates myocardial eNOS expression via the Calcineurin-NF-AT pathway

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While the importance of AT2-receptor in the myocardium is relatively uncontested, the role of the AT2-receptor has recently been subject of considerable debate. To contribute to the elucidation of this problem we investigated the influence of AT2-stimulation/inhibition on endothelial NO synthase (eNOS, NOS-III) promoter activity and eNOS protein expression in cardiomyocytes.
Stimulation of rat cardiomyocytes with angiotensin II (AngII) increased eNOS protein expression 3.3-fold. Cyclosporin A (CsA) blocked the AngII mediated increase in eNOS protein. Inhibition of the AT1-receptor did not reduce AngII mediated eNOS protein expression whereas AT2 stimulation increased it 2.4-fold and AT2 inhibition suppressed it. In gel shift assays two putative NF-AT sites in a 1.6 kb eNOS promoter fragment showed binding of NF-AT factors. NF-AT2(-c1)-specific antibodies supershifted the AngII-induced DNA binding complex. In nuclear extracts of neonatal cardiomyocytes NF-AT1, -2 and -5 were clearly detectable. Stimulation of transfected cells with AngII resulted in a 7-fold increase in eNOS promoter activity which was blocked by CsA and by mutation of an upstream NF-AT site. Inhibition of the AT2-receptor suppressed AngII induced eNOS promoter activity. Specific stimulation of the AT2-receptor increased eNOS promoter activity 4.6-fold. eNOS inhibition and simultaneous AT2-receptor stimulation increased protein synthesis as measured by 3H-Leucin incorporation.
Therefore, we conclude: 1) AngII-stimulation of neonatal rat cardiomyocytes is accompanied by increased expression of eNOS. 2) This effect is mediated by the calcineurin pathway and induced by the AT2-receptor. 3) AT2-receptor activation in the myocardium and simultaneous NOS inhibition increase protein synthesis.

P1121 Non-excitatory cardiac contactility modulation electric signals attenuate left ventricular remodelling and improve ejection fraction in dogs with heart failure

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Background: We previously showed that in dogs with heart failure (HF) LV systolic function is improved acutely with delivery of a non-excitatory cardiac contractility modulation (CCM) electric signal to the cardiac muscle during the absolute refractory period. In the present study, we examined whether long-term CCM signal delivery attenuates progressive LV chamber remodeling and sustains the improvement in LV systolic function seen with acute CCM signal delivery in dogs with HF.
Methods: Chronic HF (LV ejection fraction <35%) was produced in 12 dogs by intracoronary microembolizatons. In 6 dogs, the CCM signal delivery lead was advanced retrograde through the coronary sinus and positioned under fluoroscopic guidance into the distal anterior coronary vein. Sensing leads were also implanted in the right atrium and right ventricle and used to time the delivery of the CCM signal. In these dogs, the CCM signal was delivered for 6 hours a day with an average amplitude of 3.3 V. The remaining 6 dogs served as concurrent controls. All dogs were followed for 3 months. LV end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and end-diastolic sphericity index (EDSI) were measured from left ventriculograms obtained just before (PRE) and after 3 months of therapy (POST). Treatment effect was based on a comparison of the change from PRE to POST between the two groups.
Results: In control dogs, EDV increased from 64±5 ml to 75±6 ml ($P=0.003$), ESV increased from 46±4 ml to 57±4 ml ($P=0.003$), and EF decreased from 28±1% to 23±1% ($P=0.001$). These changes were associated with a decrease in the EDSI from 1.37±0.04 to 1.30±0.05 ($P=0.008$) indicating ongoing increase in LV sphericity. In contrast, dogs treated with CCM showed a lesser increase in EDV from 66±4 ml to 71±5 ml ($P=0.01$), no change in ESV from 46±3 ml to 47±4 ml and an increase in EF from 31±1% to 34±2% ($P=0.04$). These beneficial changes were associated with no significant changes in EDSI. Analysis of treatment effect showed that compared to controls, treatment with CCM signals significantly attenuated the increase in EDV ($P=0.04$) and ESV ($P=0.001$) and significantly increased EF ($P=0.0001$). Similarly analysis of treatment effect showed that compared to controls, treatment with CCM signals prevented the decline in EDSI ($P=0.05$).
Conclusion: In dogs with chronic HF, long-term CCM signal delivery attenuates progressive global LV remodeling and improves LV systolic function. These results support the exploration of this mode of therapy for the long-term treatment of patients with chronic HF.

P1122 Homogenization of left ventricular SERCA gene expression after myocardial infarction in the rat

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Sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) gene expression is decreased in the pressure overload-induced model of left ventricular (LV) failure in the rat and adenovirus-mediated SERCA gene transfer has been shown to restore cardiac contractile function and delay rat death. However, the level of SERCA gene expression in the non-infarcted LV following myocardial infarction (MI) remains unclear. Accordingly, we examined SERCA2a and atrial natriuretic peptide (ANP) gene expression in the remodeled non-infarcted LV after left coronary artery ligation in rats. 54 rats (21 sham-operated, 42 MI) were killed 3 months after surgery. Rats with MI were classified as nonfailing (NF, n=25) or failing (CHF, n=12) depending on the absence or presence of pleural effusion at sacrifice, respectively. The scar was carefully dissected and its surface area measured using millimeter graph paper. LV SERCA2a and ANP mRNA levels in the non-infracted LV were determined using Northern blot analysis and specific cDNA probes. We found a significant positive linear correlation between ANP mRNA and infarct size ($R^2=0.80$; $p<0.001$) whereas SERCA2a mRNA did not correlate either with infarct size or ANP mRNA. Interestingly, SERCA2a mRNA values were highly dispersed in shams (from 0.95 to 1.85 a.u.) whereas a smaller dispersion was observed in NF and an even smaller in CHF (from 0.80 to 1.10 a.u.). We conclude that LV SERCA2a gene expression is highly variable in rats and that LV remodeling following MI markedly reduces and homogenizes its level which does not correlate with ANP gene expression, a reliable marker of myocardial hypertrophy.

P1123 Prognostic significance of conventional electrocardiogram measurement in elderly patients with symptomatic heart failure

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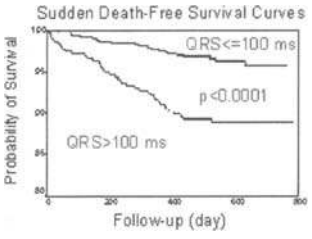
To assess the prognostic value of conventional ECG measurements in patients (pts) with heart failure, we studied 986 heart failure pts (age 71±7 year, 703 men; NYHA II-IV, LVEF <=40%) from the ELITE II trial. A 12-lead ECG, assessment of NYHA and LVEF, and serum for biochemical analysis at baseline were investigated. Heart rate (HR), mean QRS duration (QRS), maximum QT interval (QT) and maximum heart rate corrected QT interval (QTc; Fridericia's formula) were derived from each ECG. Retrospectively adjusted dichotomy limits of 460ms for QTc (QTc460) and 100ms for QRS (QRS100) were used in analyses. Of the 986 study pts, there were 140 all-cause deaths(D), 119 died of cardiovascular events(CD) and 59 died suddenly(SD) during follow-up (540±153 days). In univariate analysis, age, HR, QRS100, LVEF, NYHA, serum potassium and creatinine were significant predictors for D, also for CD except for age and potassium. For SD, QRS100, LVEF, NYHA and creatinine were univariate predictors. Neither QT nor QTc was predictive of any mode of death. In multivariate analysis (Cox model), QRS100 (p<0.001), NYHA (p=0.001), potassium (p=0.026) and creatinine (p=0.023) predicted D independently. For CD, independent predictors were: QRS100 (p<0.001), NYHA (p=0.001) and creatinine (p=0.002). Only QRS100 (p<0.001) and creatinine (p=0.023) remained independent predictors for SD. Survival analysis showed significantly reduced survival rates in pts with QRS>100ms (p<0.0001 for D, CD and SD).



Survival curves.

In this retrospective substudy, QRS>100ms independently predicted death in elderly pts with symptomatic heart failure and in sinus rhythm. If confirmed by prospective evaluation, this simple ECG measurement, in addition to other clinical variables, may provide prognostic information in this group of pts.

P1124 Reliability of non-invasive cardiac output measurement by whole-body electrical bioimpedence in patients treated for acute CHF

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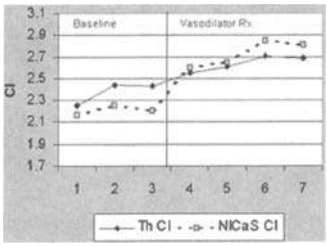
Background: The NICaS 2001TM system is an new device for non-invasive, continuous measurement of cardiac output (CO) based on whole-body electrical bioimpendence and analysis of impulse with a novel semi-empirical formula. We evaluated its reliability in monitoring patients with acute congestive heart failure (CHF).

Methods: Thirty-one patients submitted for invasive hemodynamic monitoring with Swan-Ganz catheters due to acute congestive heart failure (CHF) where enrolled in this study. Cardiac output was measure repeatedly, simultaneously and independently by NICaSTM 2001 (NiCAS-CO) and thermodilution (Th-CO). For each patient we obtained 3-4 measurements while under stable medical treatment. In 17 patients we also obtained 4 measurements per patient, while treatment with IV Isosorbide-dinitrate(ISDN) was initiated and uptitrated.

Results: Out of 31 patients, 10 where monitored while mechanically ventilated and 2 while treated by IABP. We have found good agreement between NiCAS-CO and ThCO: Linear regression is r=0.86 (p<0.05). In the subgroup of patients monitored while treated with IV ISDN, The NICaS 2001TM system correctly detected the CO increase induced by ISDN (Figure). However, we have found that the NICaS-CO reading was 6% lower than Th-CO if CI was < 2 L/min./M2 (p=0.025)and 9% higher if CI was > 3 L./min./M2(P=0.007). Therefore, the increase in CO detected by NICaSTM 2001 during ISDN treatment was twice that measured by Thermodilution (1.15 vs. 0.6 L./min, P<0.0001).



CO Changes by NiCaS and thermodilution.

Conclusions: NICaS 2001TM is a reliable device for monitoring CO in patients admitted due to acute CHF.

P1125 Differing effects of age on circadian profile of ventricular repolarization in 172 healthy volunteers

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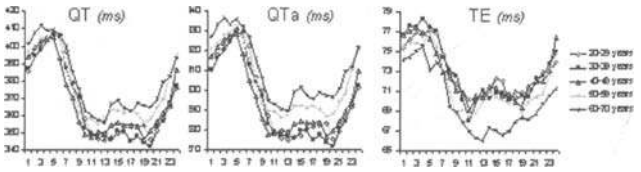
Recent studies convincingly demonstrated a limited prognostic value of spatial inhomogeneity of ventricular repolarization (QT-dispersion). However, data on physiological variations of QT-interval in the longitudinal dimension with normal aging are surprisingly rare.

Therefore we investigated 172 healthy subjects (89 females, 83 males; 38.7±15.3 years). Beat-to-beat QT-interval duration (QT, QTapex (QTa), QTc, QTac, Tend (TE)), variability (QTSD, QTaSD, QTcSD, QTacSD) and mean RR-interval were determined from 24-hour Holter monitoring after manual exclusion of artefacts and premature beats. All volunteers were fully mobile, woke up around 7 AM and had 6 to 8 hours of sleep.

Parameters of QT-interval, as well as mean RR-interval, revealed a characteristic day-night-pattern. Diurnal profiles of QT-interval variability exhibited a significant increase in the morning hours (6-19 AM; p<0.01) and a consecutive decline to baseline levels. Aging was associated with an increase of QT-interval mainly at daytime and a significant shift of the T-wave apex towards the end of the T-wave.



Circadian profiles by decade.

The circadian profile of ventricular repolarization is strongly related to mean RR-interval, however, there are significant alterations mainly at daytime with normal aging. Furthermore, the diurnal course of QT-interval variability may be related to cardiac sympathetic activity and therewith to the reported diurnal pattern of malignant ventricular arrhythmias.

P1126 QRS prolongation on surface electrocardiogram and brain natriuretic peptide as indicators of left ventricular systolic dysfunction

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Background: Prolonged QRS duration is a specific but insensitive indicator of left ventricular systolic dysfunction (LVSD). Brain natriuretic peptide (BNP) is a sensitive but only moderately specific marker of LVSD. We sought to determine, if the combination of prolonged QRS duration and BNP predicts LVSD with a higher accuracy.

Methods: We prospectively studied 128 consecutive pts (61 ± 13 years, 57 women) with suspected cardiac disease. The QRS duration on standard 12-lead resting ECG was determined. Resting BNP (pg/ml; immunoassay, Biosite Diagnostics, San Diego, USA) was obtained after 10 minutes of supine rest. BNP levels > 80 pg/ml were defined as abnormal. Left ventricular ejection fraction (LVEF) was evaluated with 2D echocardiography. A LVEF < 50% was defined as abnormal.

Results: LVEF in the LVSD group (n = 66) was 30 ± 8%, the control group (n = 62) had a LVEF of 60 ± 5% (p < 0.001).The QRS duration in the LVSD group was longer than in the group without LVSD (129 ± 34 vs. 96 ± 20 msec, p < 0.001). BNP was higher in the LVSD group than in the group with normal EF (467 ± 397 vs. 169 ± 242 pg/ml, p < 0.001). A QRS duration of > 0.1, > 0.11 or > 0.12 sec were highly specific (63%, 90%, 98%) but less sensitive (84%, 81%, 75%) for the prediction of LVSD. A BNP of > 80 pg/ml was highly sensitive (89%) but only modestly specific (55%) for the prediction of LVSD. The positive likelihood ratio for LVSD of abnormal BNP (2.0) and QRS prolongation > 0.1 sec (2.3) was improved by the combination of both criteria (5.1).

Conclusions: BNP is very sensitive but only moderately specific and QRS prolongation is very specific but less sensitive for the detection of LVSD. However, the combination of abnormal BNP and QRS prolongation yields to a higher positive likelihood ratio for the detection of LVSD compared with the two criteria alone.

P1127 Cardiac remodelling in mice after myocardial infarction followed by serial Cine MRI

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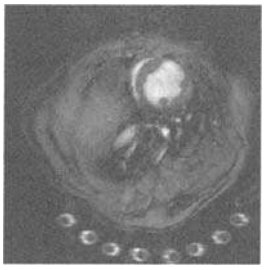
Genetically altered mice are gaining increasing importance in vardiovascular research. To further evaluate remodeling after myocardial infarction (MI) these mice will be investigated after coronary ligation. To assess the changes after MI in mice non invasivly, cine magnetic resonance imaging (MRI) was employed. MRI was performed 1 and 8 weeks after MI in a 7 T-Biospec using an ECG-triggered FLASH-sequence: 12 short axis slices, slice thickness 1 mm, echo-time 1.2 ms, resolution 230 μm. MI-size, left and right ventricular (LV&RV) volume, ejection fraction (EF), wall thickness and -thickening and LV mass were determined in 8 MI (MI size 25 ± 5%) and 5 Sham operated CBA mice. At week 1, LV mass was still equal in both groups (Sham 94.4 ± 5.5mg, MI 109.8-/-6mg), but increased significantly in MI towards 8 weeks (Sham 105.1 ± 7.9mg, MI 144.4 ± 11.7mg, $p<0.05$). LV's were larger in infarcted mice (EDV week 8: Sham 63.5 ± 4 μl, MI 94.2 μl, $p < 0.05$). In contrast, right EDV was only slightly higher in MI (Sham 62.6 ± 5.8 μl, MI 74.4 ± 7.3 μl, p=ns). EF declined in the MI group (8 weeks: Sham 69.4 -/- 2.2%, MI 46.9 -/- 5.6%, $p < 0.05$). At 8 weeks the scar was 0.5 ± 0.1 mm, which was significantly thinner than the remote wall (MI 1.1 ± 0.03 mm, Sham 0.86 ± 0.04 mm, $p < 0.05$, respectivly). Remote wall thickening was impaired in mice with MI at 8 weeks (Sham 72.5 ± 5.1%, MI 43.2 ± 9.3%, $p < 0.05$).
In conclusion, LV hypertrophy and dilatation after MI in mice was followed noninvasivly. Application of MRI to infarcted transgenic mice will shed new light on remodeling after MI.



Short axis view, anterolateral MI.

P1128 Reorganization of the cardiac connexin distribution patterns in adriamycin induced cardiomyopathy

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Background: Gap junctions, constituting of Cx(connexin)43, Cx40 and Cx45, mediate the propagation of the electrical impulse between cardiomyocytes. In human hearts Cx43 is homogeneously distributed in all chambers, while Cx40 is more abundant in atria. Advanced heart failure is accompanied by a reorganization Cx patterns. We hypothesized that adriamycin-induced cardiomyopathy is accompanied by a reorganization of the Cxs analogous to that reported for idiopathic dilated cardiomyopathy (DCM).
Methods: In FBI dogs (N=10) cardiomyopathy was induced using intracoronary adriamycin-administration (10mg/50ml saline over 1h/week). Transmural left ventricular biopsies were taken after catheter insertion (control) and 4w after adriamycin-administration. RNA was isolated and analyzed by RT-PCR for Cx43, Cx40 and Cx45. Distribution patterns were studied by immunoconfocal microscopy.
Results: In control hearts only Cx43 was detected. Adriamycin-administration led to changes in LVEDD and FS. Moderate changes (hypertrophy=HY; LVEDD: 0.21±0.21 over control; FS: 70.65±3.7% of control) were associated with increased Cx43 levels (2.46fold) and Cx40 induction. With deterioration of cardiac function (LVEDD: 0.67±0.05 over control; FS: 46.45±3.61% of control) Cx43 decreased (8.2fold), Cx40 remained elevated and Cx45 was induced. Adriamycin treated myocardium showed the typical organization of connexins in the intercalated discs and the signal intensity directly reflected the alterations observed on the mRNA expression level.
Conclusions: Adriamycin-administration resulted in a stepwise deterioration of cardiac function. Concomitantly the Cx patterns changed. First patterns arose as reported for HY and consecutively patterns as described for DCM in humans. Our data indicate that adriamycin-administration induces DCM and therefore this dog model is suitable to study effects of surgical treatment strategies of DCM such as partial left ventriculectomy on the propagation of the electrical impulse. (Deutsche Stiftung für Herzforschung, Frankfurt)

P1129 Up-regulation of gap junction protein connexin-43 in cardiomyocytes.The tool for restoration of impaired intercellular communication?

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Mechanical function of the myocardium has been shown to be markedly dependent on thyroid status and myocardial electromechanical synchronization on intermyocyte communication mediated by gap junctions. The latter ensure electrical impuls propagation and coupling that can be modulated by various endogeneous and exogeneous compounds. The study was aimed to examine whether thyroid hormone can affect expression not only contractile but also gap junction proteins and cell-to-cell junction formation.
Methods: Cultured cardiomyocytes from newborn rats with poorly developed junctions were treated on day 3 in culture with 10 or 100 nM 3,3',5-triiodo-L-thyronine (T3) and examined 48 and 72 hrs after. Incubations with monoclonal mouse anti-Cx43 and anti-alfa-sarcomeric actin antibodies followed by either goat anti-mouse conjugated with FITC or biotinylated immunoglobulin conjugated with extra avidin-peroxidase were used for immunodetection of gap junction protein, connexin-43 and alfa-sarcomeric actin, respectively. Western blot analysis was performed, as well.
Results: Immunohistochemical labeling revealed plasma membrane location of Cx-43 in punctate gap junctions, whereby the staining was much more intensive after cells exposure to T3, indicating increased number of connections. In addition, cytoplasmic staining was observed. Quantitative immunoblotting showed that T3 induced in dose-dependent manner significant increase of Cx-43 expression after 48 and 72 hrs, compared to age-matched controls. The expression of alfa-sarcomeric actin was also significantly increased, however, 72 hrs exposure to higher dosage of T3 caused mild disintegration of alfa-sarcomeric actin, warning of over-dosage.
Conclusion: The results suggest that up-regulation of gap junction protein due to T3 treatment can enhance cell-to-cell coupling. Thus, increase and/or restoration of both intercellular communication and contractility by modulation of thyroid state can be beneficial in failing heart.

P1130 Cardioprotective effect of melatonin in experimental myocardial ischaemia induced by isoproterenol in rats

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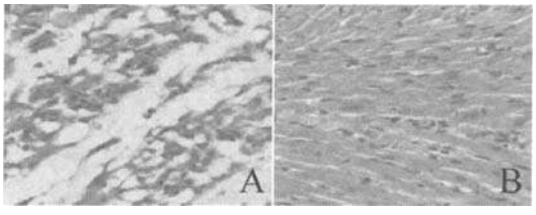
Background: Melatonin(MEL) has been found to be effective in protecting against pathological states due to reactive oxygen species release. Isoproterenol(ISO) causes severe stress in the myocardium and produces acute myocardial necrosis. This study was performed in order to determine whether MEL might protect from ischemic injury in experimental myocardial ischemia induced by ISO in rats. Methods: 24 male Sprague Dawley rats (weight 135 to 160 g) were used for this study, and divided into 3 treatment groups: (1) Control (n=8): saline only. (2)ISO (n=8): ISO (200 mg/kg/day for 2 days, s.c.). (3) MEL+ISO(n=8). MEL (10 mg/kg/day,i.p.) was started 30 minutes before the initiation of ISO, and both MEL and ISO were continued until the end of the 2nd days. The blood samples were collected for the determination of cardiac troponin T (cTnT) and cardiac troponin T (cTnI). The hearts were removed for histological examination, and observed microscopically.
Results: Plasma cTnT and cTnI levels significantly increased in ISO-treated group in comparation with controls (1.29±0.40 vs 0.46±0.21 ng/mL, $p<0.001$; 0.56±0.23 vs 0.21±0.02ng/mL, $p<0.01$ respectively). MEL+ISO-treated group showed lower cTnT and cTnI than those of ISO-treated group(0.65±0.19 vs 1.29±0.40 ng/mL, $p<0.01$ and 0.25±0.04 vs 0.56±0.23 ng/mL, $p<0.01$ respectively). MEL+ISO-treated group showed less myocardial changes on histological examinations when compared with those ISO-treated group (Pictures: Histological examination of myocardium:(A) ISO-treated rat(H.E. X200)(B)MEL+ISO-treated rat (H.E. X200).



Conclusions: The present study suggests that melatonin could have a protective effect against ISO-induced myocardial injury in rats, and a potential clinical application in the treatment of myocardial ischemia.

P1131 Overexpression of cardiac β1-adrenoceptors leads to activation of matrix metalloproteinases in vivo

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Objective: Overexpression of cardiac β1-adrenergic receptors in transgenic mice (β1-TG) leads to increased myocardial fibrosis and hypertrophy followed by left ventricular (LV) dilation. Extracellular matrix remodeling depends on collagen synthesis and collagen degrading matrix metalloproteinase activity (MMPs) and their inhibitors (TIMPs). The study investigates the role of chronic β1-adrenergic receptor activation on MMP/TIMP expression and activity during transition from hypertrophy to heart failure.
Methods: LV homogenates and mRNA of cardiac β1-TG were examined at the age of 12 weeks, 5 months and 1 year compared to wildtype (WT) FVB/N mice. The expression of collagenase MMP-13, gelatinases MMP-2,-9, membrane-type MMP (MT1MMP) and TIMPs (-1,-2,-4) as well as MMP-2 enzyme activity were measured with specific antibodies and zymographic activity assays. Picirosirius red staining was performed for collagen content and quantified with the Lucia G software.
Results: MMP/TIMP expression and activity were not altered at 12 weeks old β1-TG compared to WT. Chronic β1-adrenergic receptor activation leads to interstitial fibrosis (picirosirius red), hypertrophy and increased expression of the latent form of gelatinase MMP-2 (optical density [OD] MMP-2 latent:TG 1.2±0.1, WT 0.56±0.08,n=4,$p<0.05$), MT1MMP and TIMP-2 at the age of 5 months. This expression pattern could be responsible for activation of MMP-2 measured in failing hearts of β1-TG at the age of 1 year (OD MMP-2 active:TG 0.2±0.05, WT 0.04±0.01,n=4, $p<0.05$). Results of MMP-13, TIMP-1 and -4 measurements yielded no difference between WT and β1-TG at any time.
Conclusion: The increase of MMP activity without significant TIMP inhibition could be responsible for myocardial dilation with progressive heart failure. The study shows that transition from hypertrophy to heart failure is associated with activation of MMP-2 due to chronic β1-adrenoceptor activity.

P1132 Anti-apoptotic effect of the vasopeptidase inhibitor omapatrilat in rats with acute myocardial infarction

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Background: Omapatrilat, a vasopeptidase inhibitor, simultaneously inhibits angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP). The end result is blockade of angiotensin-II formation and inhibition of the catabolism of vasodilatory hormones, such as the natriuretic peptides, bradykinin, and adrenomedullin. The aim of the study was to compare the effects of dual NEP/ACE inhibition to selective ACE inhibition on apoptotic cell death in experimental rat myocardial infarction model.
Methods: Male Wistar rats with ligation-induced myocardial infarction were assigned to placebo or treatment with omapatrilat (10 mg/kg/day) or ramipril (1 mg/kg/day) by oral gavage starting 7 days before the induction of myocardial infarction. 2 and 24 hours post-MI the rats were sacrificed and hearts were sampled. Detection of apoptosis of cardiomyocytes from left ventricle was based on terminal deoxynucleotide transferase-mediated dUTP nick end labelling (TUNEL method).
Results: The incidence of cardiac myocyte apoptosis was significantly more reduced in the omapatrilat treated rats than in the ramipril treated rats at 2 and 24 hours after LAD occlusion (3.20 ± 0.81% at 2hr and 5.68 ± 3.14% at 24hr for omapatrilat treated rats vs 5.07 ± 2.11% at 2hr and 8.27 ± 3.73% at 24hr for ramipril treated rats vs. 8.38 ± 3.52 at 2hr and 13.97 ± 5.80% at 24hr placebo treated rats, $p<0.04$)
Conclusions: The vasopeptidase inhibitor omapatrilat prevented cardiomyocyte apoptosis after MI in rats more effectively than the ace-inhibitor ramipril. These results suggest that the vasopeptidase inhibitor omapatrilat may provide a novel therapeutic approach for cardioprotection following acute myocardial infarction.

P1133 Pulmonary congestion in heart failure contributes to increased plasma ET-1 levels by up-regulation of regional tissue ECE-1 activity

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Background: We have previously shown the pulmonary circulation to be the main source of the increased plasma endothelin-1 (ET-1) levels in a porcine model of rapid pacing induced congestive heart failure (CHF). The aim of the present study was to test if CHF is associated with an increased pulmonary conversion of the precursor hormone, big endothelin-1 (big ET-1) by endothelin converting enzyme type 1 (ECE-1) activity, and to study the effect of lung congestion on ECE-1 activity.
Methods and results: CHF pigs (n=6) which underwent rapid pacing (215-240 bpm) for 3 weeks were compared to controls (n=5). CHF-pigs exhibited significant left ventricular dilatation, reduced contractility, increased cardiac filling pressures and increased total wet weight of the lungs (696 ± 17 g/m^2 vs controls 455 ± 18 g/m^2, $p<0.001$). Plasma ET-1 increased 4-fold compared to controls ($p<0.001$) and correlated strongly with increased secretion of ET-1 in the pulmonary circulation. Plasma big ET-1 levels exhibited the highest increase (4.5-fold vs controls, $p<0.001$) in the pulmonary artery with slightly higher big ET-1 levels in the pulmonary artery than in the left ventricle of CHF animals, suggesting an increased supply of big ET-1 to the pulmonary circulation. To evaluate differences in ECE-1 activity between CHF and control animals and the influence of congestion on ECE-1 activity, we sampled lung tissue from well-ventilated upper-lobe segments, and from dependent lower-lobe segments. Lung tissue wet/dry weight ratios were highest in the dependent lower-lobe of CHF pigs (5.8 ± 0.1) compared to lower-lobe controls (5.2 ± 0.1, $p<0.01$), and upper-lobe CHF (5.3 ± 0.1, $p<0.02$), thus confirming significant congestion of the dependent lower lobes in CHF pigs. ECE activity was measured by incubating big ET-1 with solubilized lung membrane fractions with and without pre-incubation with the ECE-1 selective inhibitor FR901533, followed by quantification of ET-1 synthesis by ELISA. ECE-1 activity was highest in the congested lower lobes of CHF pigs (2.0 ± 0.3 pmol.min-1.mg protein-1) compared to lower lobe controls 1.1 ± 0.1 pmol.min-1.mg protein-1 ($p<0.02$), and to upper lobe CHF (1.1 ± 0.1 pmol.min-1.mg protein-1, $p<0.005$). ECE-1 activity correlated significantly with wet/dry weight ratios (ECE-1 activity = 1.6xwet/dry weight ratio-7.2, $R^2=0.56$, $p<0.001$)
Conclusion: ECE-1 activity is increased in congested lung tissue. Pulmonary congestion may thus be an important stimulus for the increased pulmonary ET-1 secretion which contributes to increase systemic plasma ET-1 levels in pacing induced CHF.

P1134 Growth hormone improves systolic function and myocardial bioenergetics in hypophysectomized rats

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Using hypophysectomized (hx) rats in the present study, we aimed to investigate the physiological role and mechanisms of growth hormone (GH) effects on cardiac function, geometry and myocardial bioenergetics.
Methods: Hx rats receiving hormonal supplementation with thyroxine and hydrocortisone (for three week) were used Thereafter, animals were divided into two groups: Hx group continuing the above hormonal regime, and Hx+GH group receiving s.c. injections with rhGH (1mg/kg/d),for two weeks. Intact age-matched rats were used as normal controls. Transthoracic echocardiography and in vivo 31P magnetic resonance spectroscopy were performed at the end of study. Creatine kinase (CK) activity, isoenzyme distribution were measured in heart tissue. The expression of sarcoplasmatic calcium transport ATPase (SERCA2) was evaluated.
Results: GH treatment significantly increased body weight and heart weight. Left ventricular (LV) systolic function and diastolic function were impaired in Hx group at rest and during stress compared to normal rats. Systolic wall stress (WS) was significantly higher in Hx group as compared to controls. GH treatment partially normalized systolic and diastolic LV function and significantly decreased WS. Phosphocreatine/ATP was lower in Hx-group compared with normal rats (1.68 ± 0.02 vs 2.62±.03 $p<.0001$) and was normalized with GH treatment (2.44 ±.04, $p<.0001$). Total CK activity was lower in Hx rats compared with intact rats and was not affected by GH treatment. Expression of SERCA2 was significantly lower in Hx group and partly normalized in
Conclusion: Systolic and diastolic function was significantly decreased in hx rats and normalized by GH treatment. Effects on myocardial bioenergetics and intracellular Ca^{2+} handing may be important mechanisms in the GH regulation of cardiac function and structure.

EXPERIMENTAL STUDIES IN HEART FAILURE

P1135 Therapy with the Acorn Cardiac Support Device normalizes gene expression of alpha-myosin heavy chain in dogs with heart failure

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Background: Myosin heavy chain (MHC) is a key component of the cardiac contractile machinery. Recent studies have shown that a switch from alpha-to beta-MHC isoforms takes place in myocardium of patients with chronic heart failure (HF). This switch may be partly responsible for the progressive deterioration of LV function characteristic of the heart failure state. In the present study, we examined whether chronic therapy with the Acorn Cardiac Support Device (CSD) restores gene expression of alpha-MHC in dogs with intracoronary microembolization-induced HF. Chronic therapy with the CSD has been shown to prevent progressive LV dilation and to improve LV ejection fraction in dogs with chronic HF.
Methods: The CSD, a preformed polyester device, was surgically implanted in 6 dogs with HF. Six other dogs with heart failure served as concurrent controls. All dogs were followed for 3 months. At the end of 3 months of follow-up, LV tissue was obtained from all 12 dogs and from 6 normal dogs and used to extract total RNA. Alpha- and beta-MHC isoforms were measured using reverse transcriptase polymerase chain reaction and each normalized to total MHC.
Results: mRNA for alpha-MHC was significantly reduced in untreated HF dogs compared to normals (2.9 ± 0.3 vs. 9.2 ± 1.3%, $P<0.05$); whereas mRNA for beta-MHC was significantly increased in untreated HF dogs compared to normals (97.1 ± 0.4 vs. 90.8 ± 1.6%, $P<0.05$). Chronic therapy with the CSD restored mRNA gene expression of alpha-MHC to normal levels (10.2 ± 0.6%) and decreased mRNA of beta-MHC to near normal levels (89.8 ± 0.7, %).
Conclusions: In dogs with microembolization-induced HF, LV mRNA gene expression of alpha-MHC is decreased and mRNA gene expression of beta-MHC is increased compared to normal dogs. Chronic treatment of HF dogs with the CSD normalizes mRNA gene expression for both alpha- and beta-MHC. Since alpha-MHC is a more efficient form of MHC, this normalization is likely to restore LV systolic function, albeit in part and is consistent with the observation of increased in LV ejection fraction after long-term therapy with the CSD.

P1136 Combination therapy of an endothelin receptor antagonist and an angiotensin-converting enzyme inhibitor preserves renal function in experimental congestive heart failure

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Impaired renal function, in particular, glomerular filtration rate (GFR) has recently been reported to be a stronger predictor of mortality than impaired cardiac function in advanced congestive heart failure (CHF). Endothelin (ET)-1 and angiotensin (AT)-II cause body fluid retention in CHF, however, it has not been well evaluated whether the inhibition of ET-1 and AT-II improves renal function. We administered an ET receptor antagonist (ETRA), TA-0201 alone (0.3 mg/kg/day, n=6), an angiotensin converting enzyme inhibitor (ACEI), enalapril alone (3 mg/kg/day), a combination (n=6) of TA-0201 (0.3 mg/kg/day) plus enalapril (0.3 mg/kg/day), or placebo (Control, n=6) to dogs with CHF induced by rapid right ventricular pacing (270 bpm, 3 weeks). The results are shown in the table below. Chronic treatment of ETRA or ACEI improved cardiorenal function and neurohumoral activation. Moreover, combination therapy increased GFR and prevented renal damage expressed as a further reduction of kidney weight and the expression of collagen type 1 mRNA in the kidney.

	Control	ETRA	ACEI	ETRA+ACEI
CO (L/min)	1.7±0.2	2.6±0.2 *	2.0±0.3 *	2.4±0.4 *
NE (pg/mL)	817±72	563±76 *	584±96 *	563±89 *
ANP (pg/mL)	492±50	237±18 *	390±55 *	298±29 *
UFR (mL/min)	0.24±0.05	0.37±0.04 *	0.44±0.07 *	0.52±0.12 *#
GFR (mL/min)	22.1±3.5	34.3±4.1 *	33.2±5.8 *	46.1±1.4 *#$
kidney/BW (g/kg)	4.33±0.41	3.75±0.56	3.15±0.15 *	2.32±0.11 *#$
Collagen 1/GAPDH mRNA	1.01±0.06	0.72±0.02 *	0.67±0.03 *	0.50±0.03 *#$

ETRA indicates endothelin receptor antagonist, ACEI; angiotensin coverting enzyme inhibitor, CO; cardiac output, NE; norepinephrine, ANP; atrial natriuretic peptide, UFR; urine flow rate, GFR; glomerular filtration rate, BW; body weight, Collagen 1; collagen type 1 mRNA. * $P<0.05$ vs Control, # $P<0.05$ vs ETRA, $ $P<0.05$ vs ACEI

These findings suggest that chronic inhibition of both the ET and renin-angiotensin systems may provide additional advantages by preserving renal function in the treatment of CHF.

P1137 Increase of TNF alpha-concentration in serum and liver but not in myocardium during pacing-induced heart failure in rabbits

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In heart failure (HF) patients with left ventricular (LV) systolic dysfunction, the serum TNF alpha-concentration (sTNF alpha) is increased. An increase in myocardial TNF alpha-concentration (mTNF alpha) during intracoronary TNF alpha-infusion is associated with the development of contractile dysfunction in dogs.
To study whether the increase in sTNF alpha is a cause or consequence of HF, HF was induced by rapid LV pacing (400 bpm) in ten chronically instrumented rabbits. After 3 weeks of pacing, rabbits displayed clinical signs of HF. Echocardiography revealed an increase in LV end-diastolic diameter from 15±2 to 18±2 mm and a reduction in LV shortening fraction from 35±5 to 11±4% (Mean±SEM; both $p<0.05$). Nine sham-operated rabbits served as controls. sTNF alpha, mTNF alpha and liver TNF alpha-concentrations (lTNF alpha) were measured using the WEHI-cell assay.
sTNF alpha was increased in HF rabbits compared to controls (267±27 vs. 171±24 U/ml, $p<0.05$). lTNF alpha was also increased in HF rabbits compared to controls (2215±295 vs. 1495±125 U/g, $p<0.05$). In contrast, mTNF alpha did not differ between HF rabbits and controls (700±55 vs. 625±70 U/g, ns). In the liver (HE-staining), the number of leukocytes was higher in HF rabbits than in controls (112±40 vs. 48±14 cells/mm^2, $p<0.05$). Close, linear correlations between the number of leukocytes and lTNF alpha ($r=0.78$) as well as between lTNF alpha and sTNF alpha ($r=0.68$) were demonstrated.
In this HF model with reduced LV systolic function, mTNF alpha remains unchanged. The increase in sTNF alpha appears to be a consequence rather than a cause of HF, and it is possibly a result of gastrointestinal congestion and subclinical inflammation.

P1138 Paradoxical effect of parathyroid hormone-related peptide on the hearts of spontaneously hypertensive rats

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Background: Parathyroid hormone-related peptide (PTHrP) is a peptide hormone with positive chronotropic, inotropic and dilating properties on hearts from normotensive rats. It is locally released during energy depleting conditions, like ischemia. It is not known whether PTHrP influences ventricular function in SHR in the same way than in normotensive rats. PTHrP can exert opposite effects on vascular smooth muscle cells from SHR or normotensive rats. The aim of the present study was therefore, to characterize the influence of PTHrP on ventricular function of SHR under basal and post-ischemic conditions. Methods: Isolated hearts from age matched normotensive Wistar rats and SHR were perfused in the Langendorff mode under flow constant conditions (10 ml/min). Left ventricular function was determined as developed pressure (LVDP). Hearts were perfused with synthetic PTHrP(1-36), a biologically agonist for PTHrP receptors, and D-Trp12-PTH(7-34), a PTHrP-receptor antagonist (each 100 nM). Peptides were given shortly before the onset of ischemia (30 min no-flow) to be present at the beginning of reperfusion. PTHrP concentration was determined in the perfusate. Results: No significant difference between the PTHrP release from the hearts of normotensive rats and SHR was determined at any time point. During the pre-ischemic periode, PTHrP(1-36) did not influenced LVDP in normtensive rats (123±9 mm Hg vs. 121±4 mm Hg ($n=18$), $p=0.638$) but it reduced LVDP in hearts from SHR (from 96±4 mm Hg to 83±2 mm Hg ($n=12$, $p=0.0012$)). The antagonist reduced LVDP in 5 from 6 hearts from normotensive rats (mean LVDP: 123±9 mm Hg vs. 120±3 mm Hg, $p=0.0457$) but only in 2 from 6 hearts from SHR (mean LVDP: 96±4 mm Hg to 94±9 mm Hg, $p=0.5889$). Post-Ischemic recovery was not modified by PTHrP(1-36) in hearts from either strain. In contrast, the antagonist significantly reduced post-ischemic recovery in hearts from normotensive rats from 61±9% to 17±3% ($p=0.01$), 78±5% to 36±7% ($p=0.02$), and 87±5% to 47±4% ($p=0.03$) of pre-ischemic values at 5, 15, and 30 min of reperfusion, respectively. It significantly improved post-ischemic recovery in hearts from SHR from 50±7% to 97±18% ($p=0.06$), 89±6% to 108±13% ($p=0.25$), and 95±6% to 117±8% ($p=0.01$) at 5, 15, and 30 min of reperfusion, respectively. Conclusion: The effects of PTHrP on cardiac function seem to be reversed in the SHR model of genetic hypertension. This study shows for the first time, that a single molecule may have opposite effects on cardiac function under physiological and pathophysiological conditions.

P1139 Transgenic expression of kallikrein prevents from diabetic cardiomyopathy by inhibition of ICAM-1 induction and infiltration

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We investigated the role of cell adhesion molecules (CAMs) and the kallikrein-kinin system (KLK) in experimental diabetic cardiomyopathy in rats.
Immunohistochemically stained endothelial CD54/ICAM-1 and the counter-receptor+ CD18+ and CD11a/LFA-1+ infiltrates were quantified by digital image analysis in 5μm thick cardiac cryosections in male Sprague-Dawley (SD) rats, SDSTZ rats with streptozotocin(STZ)-induced diabetic cardiomyopathy (6 weeks after STZ injection 70 mg/kg i.p.), KLK rats transgenically expressing human kallikrein and KLK rats with STZ-diabetic cardiopathy (KLK-STZ) (n=7/group). Haemodynamic parameters (LV pressure/LVP and dP/dtmax) were measured by a Millar tip catheter.
LVP (53,6 (range: 45-64) vs. 81,2 (72-90) mmHg) and the dP/dtmax (2575 (1999-3117) vs. 4656 (4200-6010) mmHg/s) were significantly reduced in SD-STZ animals compared to normoglycemic SD and KLK controls and of KLK-STZ animals. Endothelial CD54/ICAM-1 expression and infiltrate density were significantly increased in STZ-rats compared to normoglycemic controls and KLK-STZ rats (table). Infiltrates and CAMs-expression correlated significantly with LVP and dP/dtmax ($p<0.05$).

	SD-rats	KLK-rats	KLKSTZ-rats	SDSTZ-rats
CD54	0.03 (0.02-8)	0.05 (0.03-6)	0.03 (0.02-7)	0.17 (0.09-26)
CD18	23.6 (17-25)	26.8 (20-30)	27.4 (19-33)	59.6 (43-72)
CD11a	8.3 (5-11)	8.6 (4-10)	10.1 (6-14)	22.6 (20-26)

Our data indicate that inhibition of CAMs-induction and of the consequent counter-receptor+ immunocompetent infiltration constitutes a relevant mechanism by which transgenic activation of the KKS prevents from LV contractile dysfunction in experimental diabetic cardiomyopathy.

P1140 Reverse left ventricular remodelling with the Acorn Cardiac Support Device in dogs with advanced heart failure: a randomized, placebo controlled study

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Background: Chronic progressive left ventricular (LV) chamber remodeling in patients with heart failure contributes to progressive LV dysfunction. We previously showed that in dogs with moderate heart failure, the Acorn Cardiac Support Device (CSD), a preformed polyester device that is surgically fitted over the cardiac ventricles, prevents progressive LV remodeling. In the present study, we examined the effects of the CSD on reversal of progressive LV remodeling in dogs with advanced HF (LV ejection fraction, EF <27%).
Methods: Advanced heart failure was produced in 13 dogs by multiple sequential intracoronary microembolizations. Dogs were randomized to monotherapy with the CSD (n=6) or to a sham surgical procedure (Control, n=7). All dogs were maintained for 6 months following surgery. LV end-systolic volume (ESV) and end-diastolic volume and LV EF were measured from left ventriculograms performed at the time of randomization (PRE) and at the end of 6 months of follow-up (POST). Evaluation of treatment effect was based on a comparison between the two study arms with respect to the change between PRE and POST treatment values.
Results: Of the 7 dogs randomized into the control arm, 2 died prior to completion of the 6 months follow-up period; one from congestive heart failure and one from sudden cardiac death. All of the dogs randomized into the CSD-treatment arm survived the entire duration of the study. In the 5 control dogs that survived, LV ESV increased from 55 ± 4 ml to 69 ± 6 ml (P=0.007), LV EDV also increased from 74 ± 6 ml to 85 ± 6 ml (P=0.0004) and LV EF decreased from 25 ± 1% to 19 ± 1% (P=0.014). In contrast, in CSD-treated dogs, LV ESV decreased from 58 ± 5 ml to 51 ± 3 ml (0.005), LV EDV decreased from 78 ± 6 ml to 69 ± 5 ml (P=0.003) and LV EF tended to increase from 25 ± 1% to 27 ± 1% (P=0.18). Analysis of treatment effect showed that compared to controls, treatment with the CSD significantly reduced ESV (P=0.0001)and EDV (P=0.0001) and prevented the progressive decline of EF (P=0.001).
Conclusions: In dogs with advanced heart failure, long-term therapy with the Acorn CSD elicits reverse LV remodeling in association with prevention of progressive LV systolic dysfunction. These results support our findings in dogs with moderate heart failure.

ASSESSING VIABLE MYOCARDIUM: CURRENT PERSPECTIVES

P1141 Comparison of low dose DSE and echocardiography during GIK infusion for the detection of myocardial viability after anterior myocardial infarction

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Background: Low dose dobutamine stress echocardiography (LDDSE) is one of the method most used to assess myocardial viability. Glucose-insulin-potassium(GIK) has been shown to increase contraction of the ischeamic zone.
Objectives: We aimed to compare LDDSE and echocardiography during GIK infusion for detecting myocardial viability.
Methods: Thirthy two patients who had first anterior myocardial infarction (MI) and without previous MI were included in the study. Echocardiographic evaluation was carried out on the 7th ±2 days after MI. Intravenous infusion of dobutamine(3mg/kg body weight/min) was started and continued for 5 minutes and than increased to 5mg/kg/min and 10mg/kg/min for another 5 minutes. Glucose-insulin-potassium protocol consisted of fixed dose of insulin(100mU/kg/hour iv) and a variable glucose/potassium infusion rate. GIK echocardiography was made at baseline and after 60 minutes of GIK. The detected viable myocardium was defined as 1 or 2 scores decreasing in at least two adjacent abnormal segments during LDDSE and GIK echocardiography.
Results: Viability was detected in 20%(57 segments) of the asynergic segments at baseline with GIK echocardiography and 22%(62 segments) of those segments with LDDSE($p>0.05$). Left ventricular wall motion score index at baseline was 1.87 and it decreased significantly during both LDDSE and GIK echocardiography ($p<0.001$, vs 1.75 and 1.76 respectively). The agreement between LDDSE and GIK echocardiography for detection of myocardial viability was 96%.
Conclusion: We have shown that GIK augments the myocardial contractility after anterior MI in viable segments. The high agreement between LDDSE and GIK echocardiography suggests that GIK can be used to detect myocardial viability after acute MI

P1142 Ischaemic preconditioning protects myocardium against reperfusion injury by attenuating Ca^{2+}-induced cell fragility

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The wealth of knowledge on the triggers and signal transduction systems involved in the genesis of the protective effect of ischemic preconditioning (IP) against cell death secondary to ischemia-reperfusion is in striking contrast with the lack of information regarding the effectors mechanisms responsible of the protection. Here we investigated whether these effectors act during ischemia or during reperfusion. The effect of IP (two cycles of 5 min of ischemia/5 min reperfusion) were analyzed in isolated, isovolumetric contracting rat hearts (n=16) submitted to transient (60 min) ischemia. IP had no beneficial effect during ischemia; on the contrary, it accélerated ATP depletion (from 7.7±0.8 μmols to 5.1±0.6 μmols measured 10 min after onset of ischemia, p=0.041), the onset of ischemic rigor (increase in LV diastolic pressure (LVDP), from 11.9±0.4 min to 5.8±0.5min, $p<0.001$), and electrical uncoupling (tissue electrical resistivity, from 10.2±0.4 ohms x cm to 8.7±0.5 ohms x cm, p=NS). In contrast, IP protected against reperfusion-induced hypercontracture (increase in LVDP, 140.2±6.3 mmHg in control hearts vs. 106.2±2.9 in IP hearts, p=0.001), LDH release (52.0 U/gdw in control hearts vs. 13.8 U/gdw in IP hearts, $p<0.001$), and improved functional recovery (10.0±4.2% in control hearts vs. 47.4±7.2% in IP hearts, $p<0.001$. The effect of IP was then studied in 18 hearts submitted to Ca^{2+} overload by removing Na^+ from the perfusion buffer (osmolarity maintained with mannitol), and then to cell swelling by reintroduction of Na^+ during normoxic conditions. This protocol resulted in no LDH release during Na^+ deprivation, and in severe myocardial edema, LDH release and impairment of contractile function (pulse pressure 33% respect to basal) upon reintroduction of Na^+. This effects were markedly attenuated by inhibition of NCX1 with KB-R7943 during Na^+ deprivation, or by increasing osmolarity with mannitol during reintroduction of Na^+. Application of IP before deprivation of Na^+ did no attenuate edema associated to reintroduction of Na^+, but markedly reduced LDH release (44.0±3.3 U/gdw vs. 23.9±4.1 U/gdw, p=0.010) and contractile failure (pulse pressure 57% respect to basal, $p<0.001$). These results suggest that IP protect against cell death during reperfusion by attenuating cell fragility secondary to Ca

P1143 Heat stress and ischaemic preconditioning produce similar patterns as regards p38 MAPK and JNKs activation in the isolated rat heart

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Introduction: Heat stress (HS) has been shown to protect the heart against ischaemia; however apart from heat shock protein increase, its mechanism has not been thoroughly investigated. In order to identify possible mechanisms of HS induced cardioprotection we studied the activation pattern of p38 MAPK and JNKs, intracellular protective molecules and compared it to that of ischaemic preconditioning (IP).
Methods: 1. Wistar rats were subjected to whole body HS at 42°C for 15min (HEAT) or sham anesthesia (SHAM). 24hours later their hearts were perfused in the Langerdorff mode and subjected either to 20min of stabilization (HEAT-BASE, n=4 and SHAM-BASE, n=4) or 20min of stabilization followed by 20min zero-flow global ischaemia (I) and 45min of reperfusion (R) (HEAT-I/R, n=9 and SHAM-I/R, n=8). The postischaemic recovery of function was assessed by the recovery of of left ventricular developed pressure (LVDP) expressed as % of the initial value (LVDP%). 2. After 20min of stabilization, isolated hearts were subjected to 4 cycles of PC (3min I, 5min R and 3 cycles of 5min I and 5min R) followed by 20min of I and 45min of R (PC-I/R, n=6) and compared to control hearts (CONT-I/R, n=6). 3. Phosphorylated and total p38 MAPK and p54 and p46 JNKs were measured by Western blot analysis at the end of I/R. These proteins as well as HSP70 were measured at HEAT-BASE and SHAM-BASE.
Results: 1. LVDP% was higher in HEAT-I/R compared to SHAM-I/R [60.3(6.3) vs 42.9(4.1), $p<0.05$]. In addition LVDP% was higher in PC-I/R than in CONT-I/R [59.17(4.67) vs 37.22(4.5), p,0.05]. 2. In SHAM-BASE HSP70 was not detectable while it was induced in HEAT-BASE hearts. Phospho-p38, p38, phospho-JNKs and JNKs were not different between SHAM-BASE and HEAT-BASE. 3. Phospho-p38 was not different between SHAM-I/R and HEAT-I/R and was non-significantly less in PC-I/R than in CONT-I/R, p=0.09. 4. Phospho-p54 JNK was 1.45fold higher in SHAM-I/R than in HEAT-I/R, $p<0.05$ and phospho-p46 JNK was 1.6fold higher in SHAM-I/R than in HEAT-I/R, $p<0.05$. Moreover phosphorylated p54 JNK was 1.85fold higher in CONT-I/R than in PC-I/R, $p<0.05$ and phosphorylated p46 JNK was 2.0fold higher in CONT-I/R than in PC-I/R, $p<0.05$.
Conclusion: HS induced cardioprotection is associated with attenuated activation of JNKs, but not p38 MAPK, in response to ischaemia and reperfusion. This pattern is identical to that produced by IP.

P1144 Prognostic importance of myocardial viability in revascularized patients with coronary artery disease and left ventricular dysfunction

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The aim of this study was to assess the prognostic value of the amount of dysfunctional but viable myocardium in revascularized patients with chronic coronary artery disease (CAD) and left ventricular (LV) dysfunction.
Methods: Four hundred and thirty-one consecutive patients with chronic CAD and LV ejection fraction of 40% or less underwent low-dose dobutamine echocardiography for viability assessment. To quantify the amount of dysfunctional but viable myocardium, wall motion was scored using a 16-segment model. Two hundred and twenty patients were revascularized and followed up for a mean period of 33 ± 23 months (range, 0 to 86) for cardiac-related death and hospitalization for heart failure.
Results: Receiver operating characteristic curve analysis identified 6 dysfunctional but viable segments as the optimal cutoff value for discriminating patients with and without risk of cardiac events. Thirty-eight patients exhibited a large amount of dysfunctional but viable myocardium (6 segments or more, group A), 103 patients had 2-5 dysfunctional but viable segments (group B), and 79 patients were found to have dysfunctional myocardium irreversibly damaged (group C). Similar baseline LV ejection fractions of 36 ± 4%, 34 ± 5%, 35 ± 5% in groups A, B, and C increased to 46 ± 6% ($p < 0.01$ vs baseline and vs groups B and C), to 39 ± 5% ($p < 0.01$ vs baseline and group C), and to 36 ± 7% ($p < 0.01$ vs baseline), respectively, after revascularization. The greatest functional improvement after revascularization in group A patients was accompanied by a lower frequency of cardiac events during follow-up (1 vs 27 in group B, $p < 0.01$, and vs 18 in group C, $p < 0.01$) and by a better cardiac event-free survival according to Kaplan-Meier survival analysis ($p < 0.01$ vs groups B and C, respectively).
Conclusion: In revascularized patients with CAD and moderate-to-severe LV dysfunction, the presence of 6 or more dysfunctional but viable myocardial segments identifies patients with the best prognosis.

P1145 Preconditioning alters mitochondrial transition pore opening in the rabbit heart

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Mitochondria permeability transition (MPT) seems to be a pivotal event in both necrosis and apoptotis. Recent studies suggest that preconditioning, that has antinecrotic and antiapoptotic effects, may protect the myocardium through modulation of mitochondrial metabolism. The aim of the present study was to determine whether preconditioning might influence permeability transition pore opening. NZW rabbits underwent either no intervention (sham, n=7) or 10 min. of ischemia and 5 min. of reperfusion. Before ischemia/reperfusion, rabbits underwent either no intervention (control, n=8) or 5 min.ischemia/5 min. reperfusion (PC, n=6). The area at risk of these hearts were rapidly harvested at the end of this protocol. Mitochondria were isolated using differential centrifugation and suspended in an isolation buffer. Integrity of the mitochondria was checked using electronic microscopy. Mitochondrial Ca^{2+} uptake and release was measured as a change in the free Ca^{2+} concentration within the suspension using a calibrated Ca^{2+} - selective minielectrode. Pore opening was defined as the massive released of Ca^{2+} by mitochondria in the suspension following Ca^{2+} overload. Specifically, we measured the total Ca^{2+} load necessary to open the pore and time to pore opening. Data are expressed as % of sham. *$p<0.05$ vs control, *$p<0.05$ vs sham (table).

	sham	control	preconditioned
total Ca^{2+} load (%)	100	67±9 †	79±10 †*
time to pore opening (%)	100	69±8 †	77±12 †*

In the control group, both total Ca^{2+} load and time to pore opening were significantly reduced versus sham. Interestingly, preconditioned mitochondria needed a higher Ca^{2+} load to open the permeability transition pore and displayed a delayed pore opening when compared to controls. These data suggest that preconditioning may modulate mitochondrial transition pore opening in the rabbit heart.

P1146 Chronic hypoxic preconditioning modulates nitric oxide synthase expression and improves post-ischaemic recovery in isolated working rat hearts

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Background: several studies reported that chronic hypoxia may induce a preconditioning against ischemia in the heart. The mechanism of chronic hypoxic preconditioning is unknown; it appears to be different from that of classic ischemic preconditioning. The chronic hypoxic preconditioning involves the transcription of mRNA and subsequent synthesis of certain protective proteins, including antioxidant proteins. We tested the hypothesis that the cardioprotection exerts by chronic exposure to hypoxia is associated with an increase in antioxidant enzyme activity induced by the initial oxidative stress. Methods: Wistar rat hearts were used for experimental procedure, and divided into two groups: A) Normoxic; B) Hypoxic (maintained in a chamber filled with 10% oxygen for 2 weeks). Haemodynamic parameters (coronary and aortic flows, heart rate, aortic pressure, minute work and coronary resistances), heart weight changes, creatinekinase (CK) release in coronary effluent and microvascular permeability (FITC-albumin extravasation) were evaluated. In addition, endothelial and inducible nitric oxide synthase (eNOS and iNOS) gene expressions were estimated by rt-PCR, and eNOS and iNOS protein levels were detected by Western blot analysis. SOD activity was evaluated by spectrophotometric method. Results: in normoxic hearts a significant functional damage, necrosis enzyme release and ultrastructural damage were detected. Hypoxic hearts showed significantly reduced I/R damage (decreased enzyme release and reduction of post-ischemic myocardial edema and ultrastructural alterations) compared to A group. The e-NOS mRNA and protein levels were significantly higher in groups B, while i-NOS mRNA and protein levels were less expressed respect control group. SOD activity was higher in hypoxic hearts (basal: A: 37 U/mg ± 3, B: 40 U/mg ± 4; after I/R A: 39 U/mg ± 5, B: 50 U/mg ± 6, $P<0.02$ vs basal and A). Conclusions: our data suggest that the chronic exposure to hypoxia preserves e-NOS gene expression, reduces i-NOS postischemic overexpression and increases SOD activity; these effects, able to reduce cellular oxidative stress, may be responsible for the observed cardioprotection against ischemia-reperfusion injury.

P1147 Dobutamine-induced contractile reserve in stunned, hibernating, and scarred myocardium in patients with ischaemic cardiomyopathy

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Aim: Due to chronic exhaustion of cardiomyocytes and damage of the contractile apparatus, contractile reserve may be observed less frequent in hibernating than in stunned myocardium. The aim of this study was to assess the presence of contractile reserve in response to dobutamine infusion in a large group of patients with stunned and hibernating myocardium.
Methods: A total of 198 consecutive patients with ischemic cardiomyopathy (LVEF<40%), underwent F18-fluorodeoxyglucose SPECT imaging to assess myocardial perfusion and glucose metabolism. Contractile reserve was evaluated by dobutamine stress echocardiography. Dysfunctional segments (identified by resting echocardiography) were subsequently evaluated for viability. Dysfunctional segments with a normal perfusion were considered stunned myocardium. Dysfunctional segments with a perfusion defect and a relatively increased FDG uptake were considered hibernating. Dysfunctional segments with concordantly reduced Tc-99m-tetrofosmin and FDG uptake were considered scar. Subsequently, these segments were divided into nontransmural scars (tracer activities of >50%) and transmural scars (tracer activities <50%)
Results: Dobutamine-induced contractile reserve was more frequently found in stunned than in hibernating myocardium (61% versus 51%, respectively, $p<0.01$). Only 14% of the scarred segments improved in wall motion during dobutamine infusion, this was considerably less often than the contractile reserve seen in stunned or hibernating myocardium ($p<0.001$). Moreover, nontransmural scar more often exhibited contractile reserve than transmural scar tissue
Conclusion: The progressive reduction of contractile reserve in stunned, hibernating, and scar tissue, supports the hypothesis that stunning, hibernation, and scar are not circumscript pathophysiological entities but represent gradual ultrastructural damage on the myocyte level.

P1148 Oral nicorandil recaptures the waned protection of preconditioning in vivo

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Protection from preconditioning (PC) wanes and is eventually lost when multiple bouts of short ischemia (isc) or a prolonged reperfusion (rep) interval preceeds the following sustained isc. The activation of mitochondrial KATP channels plays a pivotal role in the intracellular signaling of PC. We tested whether the specific KATP channel opener nicorandil (nic) preserves the given protection from PC in conditions where this benefit decays and is lost.
Methods: Eight groups of male rabbits (n=6-7/group) were divided in 2 equal series of experiments: one series without (-) and one with (+) oral nic treatment. Nic was given for five consecutive days in a dose of 5 mg/kg/d, and the last dose was given a few hours before the isc. All the animals were anesthetized and then subjected to 30 min regional myocardial isc and 2 hours rep with one of the following interventions before the sustained isc: control groups C to no intervention; 3PC groups to 3 cycles of 5 min isc/10 min rep; 8PC groups to 8 cycles of 5 min isc/10 min rep and 3PC90 groups to the same interventions as the 3PC groups but with a prolonged (90 min) intervening rep interval before the sustained isc. The infarcted (I) and the risk areas (R) were defined with TTC staining and Zn-Cd fluorescent particles and their ratio was expressed in percent (%I/R).
Results: The infarct size in %I/R is shown in the table.

	Group C	Group 3PC	Group 8PC	Group 3PC90
Nic(-) series	41.5±4.7	10.3±3.4	47.7±8.8	37.3±6.0
Nic(+) series	43.9±7.1	12.2±3.9	13.0±2.6*	14.2±2.4*

* $P<0.01$ vs respective groups of Nic(-) series.

Conclusion: Nic recaptures the waned protection of PC, both after repetitive bouts of short isc or after a prolonged rep interval, preserving the initially obtained benefit. Nic, by itself is not sufficient to initiate PC in vivo.

P1149 Direct epicardial mapping predicts the recovery of chronically ischaemic dysfunctional myocardium

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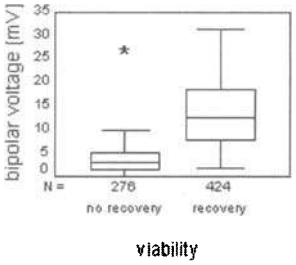
Background: The preoperative assessment of myocardial viability is crucial in the planning of revascularization procedures in patients with coronary artery disease (CAD). Therefore, this study investigated the value of direct bipolar epicardial mapping immediately before CABG in the differentiation of viable from non-viable myocardium.
Methods and Results: In 34 patients with CAD a maximum of 102 bipolar epicardial electrograms per patient (n=3,468 electrogramms) were recorded intraoperatively simultaneously with a ventricular jacket array. In accordande to the position of each electrode segmental myocardial function (echocardiography) was assessed before and 3 months after CABG using a wall motion score. Only electrodes with good myocardial contact (n=1,813, 52±14 per patient) were considered. Based on the echocardiographic findings at baseline and following CABG segments preoperatively dysfunctional segments (n=700) were classified as viable (improvement of at least 20%, n=424) or non-viable (no improvement, n=276). Bipolar voltage was significantly lower in non-viable when compared to viable myocardium (Fig. 1: *: $P<0.001$, ANOVA) ROC-curve-analysis for bipolar voltage to discriminate between viable and non-viable myocardium revealed a sensitivity of 83% with a specificity of 83% and an area under the ROC-curve of 0.92 at a cut-off value of 5.9 mV.



Conclusion: Viable myocardium can correctly be differentiated from non-viable myocardium by direct epicardial mapping. Based on these findings in future, viability myocardium may be detectable by body surface mapping techniques using inverse solutions.

P1150 Dynamic and low-dose dobutamine stress echocardiography in the assessment of late doxorubicin-induced cardiotoxicity

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Background: Late cardiac toxicity of doxorubicin has been a serious side effect of the anticancer treatment. The development of anthracycline cardiomyopathy late after successful completion of chemotherapy can substantially worsen the perspective of these patients.
Aim of study: The aim of present study was to assess the value of low-dose dobutamine stress test and dynamic stress echocardiography in the detection of early changes of LV function in asymptomatic survivors treated for childhood cancer.
Methods: Dobutamine was administered four minutes in two periods: 5 - 10 ug/kg/min and echocardiographic examination was performed before and at the top. We have calculated parameters of LV systolic function: EF, FS, mVcfc, endsystolic wall stress (ESS); global function: MPI (Tei index); diastolic function: E/A ratio, DT and IRT. Ejection fraction was measured before and immediately after symptom-limited dynamic stress echocardiography.
Patients: All patients completed successfully chemotherapy and were in long-term remission of the disease with a good quality of life comparable to the controls. The time of follow-up was 7+3 yrs. 69 patients (15+5 yrs) underwent the dynamic stress and 36 patients (12+5 yrs) also pharmacological stress test. The mean cumulative dose of administered doxorubicin was 226+106 mg/m^2. The control group consisted of 20 volunteers (12 male, 8 female, 12+4 yrs).
Results: We have not found any changes in exercise tolerance and hemodynamic response to the dynamic stress between patients and controls. The exercise increment of EF was also similar (15+5%/14+4%, n.s.). Dobutamine has not influenced heart rate and diastolic blood pressure in any subgroup but slightly increased systolic blood pressure. The patients differed significantly in mVcfc ($p<0.05$), MPI ($p<0.02$), ESS ($p<0.04$) and IRT ($p<0.05$) at rest in the comparison to the controls. The administration of dobutamine has confirmed these differences in MPI ($p<0.001$), ESS ($p<0.05$) < and IRT ($p<0.05$). 63% of the patients revealed a pathological response of one or more variables to the dobutamine, which was not observed in the controls
Conclusions: Despite normal findings during dynamic stress echocardiography, low-dose dobutamine stress test proved to be a very sensitive method for the detection of early subclinical changes in LV function in children and adolescents after the treatment with doxorubicin. The clinical value of these changes has to be assessed during the long-term follow-up.
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P1151 Improve detection of myocardial viability by rest GIK-^{99m}Tc-sestamibi comparison with Tl-201 reinjection,in post myocardial infarction patients

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The ability of Tl-201 imaging to detect potential reversibility of severe regional perfusion defects after rest injection and thallium reinjection techniques have been compared with the use of NTG- MIBI protocols achieving similar results for detecting exercise perfusion defects reversibility. GIK solutions could improves electrical and mechanical performance, preserving intracellular adenosine triphosphate concentrations and myocardium viability after acute infarction. Methods and results: forty four patients (32 men, 12 women mean age 57.33±12.84 years) with previous myocardial infarction (mean evolution 4.7±3.4 months) underwent pharmacological stress (dipiridamole), redistribution and reinjection Tl-201 imagine as well rest Tc-99m Sestamibi, after the intravenous administration of GIK (200 gr. Glucose + 30 UI regular insuline+ 40 mEq potassium cloride/500ml in continuous infusion during 3 hr.), Group A (n=14) or oral administration of 70 gr. of glucose + 40 mEq of potassium cloride taking in advantage the endogenous insulin secretion, to non-diabetic patients (Group B, = GB, N=15) and group C (GC, diabetic patients N=15).All of the 44 patients received 10 mg of sublingual isorbide previous to 25 mCi of Tc- 99m Sestamibi in different 2 days protocol. A total a 880 myocardial segments were assessed and number and severity of perfusion defects in segments involved, supplying by anterior descending (LAD), right coronary (RC) and Circumflex (Cx) arteries according to follow: score normal=0, hipoperfusion, mild= 1, moderated =2, severe =3 and the average were compared between Thallium 201 re-injection and GIK- MIBI. Involved territories number: 4.12 ± 2.60 vs 6.78 ± 2.02, p =0.005 for AD; 5.4 ± 1.46 vs6.34 ± 1.01, p =0.05 for RC and 1.60 ± 1.10 vs 2.07 ± 1.04, p= 0.05 Cx. For GIK-MIBI vs Tl-201 reinjection respectively, and defect severity: 8.4 ± 6.17 vs13.68± 5.43, p= 0.01 for LAD; 11.92 ± 5.18 vs 15.13± 4.65, p= 0.005 for RC and 2.71± 2.16 vs 4.73 ± 3.48, p= 0.003 Cx. For GIK-MIBI vs Tl-201 reinjection respectively. Conclusion: Our data suggest that GIK-MIBI protocol is a safe and easy procedure that improve the detection of perfusion reversible defects compared with Tl-reinjection getting better information about myocardial viability, with lower cost and acquisition time.

P1152 Dobutamine-response of Doppler myocardial performance index: a marker of viable myocardium and coronary artery disease

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Aim: Dobutamine stress echocardiography (DSE) remains a subjective technique. Systolic and diastolic Doppler time interval assessment (Doppler myocardial performance index or MPI) during DSE may represent an objective adjunct to potentially recognize both viable and ischemic myocardium.
Methods: Fifty-five consecutive patients, mean (±SD) age 64 ± 4 years, with ischemic left ventricular dysfunction (mean ejection fraction 38 ± 6%), underwent DSE for assessment of myocardial viability and ischemia. Pulsed-wave Doppler of mitral flow and left ventricular outflow tract (ejection time) was recorded at each stage of DSE at a sweep rate of 100 mm/s. Isovolumic interval was obtained by subtracting ejection time from inter-mitral interval. MPI was calculated off-line as isovolumic interval divided by ejection time. Patients with significant arrhythmias, mitral or aortic valve disease, diastolic restrictive pattern and excessive loading reactions to DSE were excluded. Tl-rest-redistribution SPECT for myocardial viability was performed. At coronary angiography was defined significant a stenosis >70% of lumen diameter of epicardial coronaries (>50% of left main coronary artery).
Results: Resting MPI correlated to both extension and severity of resting myocardial dyssynergy (r <0.74). During DSE a cut-off <0.07 shortening of MPI at low dose (10μg/kg/min of dobutamine) predicted myocardial viability as detected by Tl-rest-redistribution: agreement 68%, kappa 0.15. At peak dose of DSE lengthening of MPI (cut-off >0.14) predicted coronary artery disease (CAD): agreement 78%, kappa 0.35. During all steps of DSE a biphasic pattern of MPI correlated to a biphasic wall motion pattern, thus allowing recognition of myocardial ischemia (r = 0.85).
Conclusions: In patients with ischemic left ventricular dysfunction, MPI calculated during DSE appears an objective and easy-to-measure marker of viable myocardium. An accurate prediction of MPI appears also for CAD and myocardial ischemia. MPI appears a promising objective adjunct during the main stages of DSE.

TREATMENT OF HYPERTENSION

P1153 Antioxidant status in essential arterial hypertension during therapy with Amlodipine

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Background: Recent studies demonstrated that calcium-antagonist amlodipine inhibits lipid peroxidation, suggesting an intrinsic antioxidant activity of this drug, which may explain its higher efficacy in the medical practice. Aim of the present study was to evaluate with a new analytical assay the total plasmatic antioxidant activity in patients with essential hypertension treated with amlodipine.
Methods: The total plasmatic antioxidant activity as the ability to antagonise the oxidation of a-keto-g-methiolbutyric acid by both peroxyl and hydroxyl radicals (obtained through thermal decomposition of an azo-bis precursor and a modified Fenton reaction) was measured in 15 patients (9M, 6F, range 44-60 years) with essential hypertension in wash-out and after 6 weeks of treatment with 10 mg/die of amlodipine and compared with that of 15 age-sex-matched controls. The results are expressed as TOSC (Total Oxyradical Scavenging Capacity) units.
Results: At follow-up visit after 6 weeks, patients showed systolic blood pressure (148.4±9.2 vs 130.2±8.6 mmHg, p<0.001) and diastolic blood pressure (98.8±6.3 vs 82.4±5.4 mmHg, p<0.001) significantly reduced, while heart rate did not significantly differed from baseline (70.4±6.8 vs 72.6±8.9 bpm, ns). The total plasmatic antioxidant activity at baseline was significantly lower in patients with hypertension than control subjects (TOSC 25.2±7.7 vs 32.6±4.5, p<0.01); at follow-up visit, after treatment with amlodipine, patients showed a significant improvement of scavenging capacity (TOSC 33.8±5.2 vs 25.2±7.7, p<0.001), while controls did not modify their antioxidant efficiency (TOSC 32.6±4.5 vs 31.9±4.2, ns).
Conclusion: The results of this study confirms an intrinsic antioxidant activity of amlodipine. We may hypothesise that, for the combined anti-hydroxyl and anti-peroxyl activity, amlodipine seems to be useful in hypertension because it decreases oxidative stress, and normalize of pressure values.

P1154 Differential effect of antihypertensive drugs on pulse pressure

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Aim: Pulse pressure (PP) is emerging as a major predictor of cardiac risk. The results of antihypertensive (AH) treatment have mostly included systolic and diastolic blood pressure changes (SBP, DBP) but not PP. This paper explores PP changes in a large cohort of hypertensive patients.
Methods: We examined 10185 consecutive patients, 5395 men and 4790 women 56±13 years old, with uncomplicated essential hypertension, after a 15-day wash-out period and after 6 months of antihypertensive monotherapy. All patients included in the final cohort had normalized their blood pressure. % SBP, DBP and PP changes were calculated and compared.
Results: PP was decreased least with diuretics and most with angiotensin II receptor antagonists (AIIRA), followed by Ca-antagonists and ACEI (p< 0.0001 as compared to diuretics, α-blockers, β-blockers). These differences were accounted by a greater decrease of SBP with those 3 drug families (p<0.0001) (table).

Changes in %ΔPP, %SBP,%DBP

Rx	n	%Difference PP	%SBP	%DBP
Diuretics	560	-13±22	-18±8	-22±8
a-blockers	454	-23±22	-21±9	-20±8
b-blokers	2190	-26±25	-23±9	-22±7
Ca antagonists	3223	-34±27	-27±11	-23±8
ACEI	2260	-30±24	-25±9	-22±7
AIIRA	1498	-45±27	-31±10	-24±7

Conclusion: Among AH drugs used for monotherapy, AIIRA, ACEI and Ca-antagonists decrease PP most. Since PP has adverse prognostic implications, these differences may be of practical value.

P1155 Beta blocker therapy has favorable effects on serum homocyteine levels

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Background: It has been shown that serum levels of homocysteine is elevated in hypertensive patients. In one report of hypertensives, studying the relationship with high homocysteine levels and atherothrombosis, it was observed that serum homocystein levels were lower in patients on beta blockers. Also in neuron astrocyte cultures, beta adrenergic stimulation caused homocyteinic acid secretion, and this was blocked by concominant use of atenolol. These data led us to investigate if beta-blockers has an homocysteine lowering effect. We also tested if the diuretic spironolactone with anti-aldesterone properties also has this effect or not.
Methods: To investigate this hypothesis we enrolled newly diagnosed 65 hypertensive patients who had not used any medication. Patients were requried to have no medical problems apart from essential hypertension and have normal serum vitamin B12 and folat levels. Patients were randomized to either spironolactone 50 mg/day or metoprolol 100 mg/day. No other medications were allowed during the 5 month follow-up. If their blood pressures were not normalized (< 140/90 mmHg) doses of both drugs were doubled. Serum biochemistry and homocystein levels were investigated at baseline, 1 month and 5 months after the commencement of therapy.
Results: There were 41 patients (17 men and 24 women; mean age, 49.4±9.7 years) in metoprolol group and 24 (5 men and 19 women; mean age, 48.8±6.5 years) in spironolactone group. Drug doses had to be increased in 14 (34%) individuals in the metoprolol group, and in 10 (42%) patients in the spironolactone group ($p>0.05$). In patients receiving metoprolol serum homocystein levels decreased in the 1st month and this was more pronounced in the 5th month (from 13.5 ± 4.4 to 12.4 ± 4.0 to 11.9 ± 2.5 μmol/L, $p = 0.011$). In spironolactone group there was not a significant change from the baseline both on the 1st and 5th months (from 13.6 ± 8.3 to 13.1 ± 5.4 to 13.2 ± 5.0 μmol/L, $p> 0.05$).
Conclusions: The data suggest that the selective BB metoprolol decreases plasma homocysteine levels in hypertensive patients, whereas spironolactone does not have this effect. This preliminary observation however needs to be tested in larger trials.®

P1156 Intravenous enalaprilat in hypertensive emergencies complicated with left ventricular failure

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Little and controversial information is available concerning the use of intravenous (i.v.) enalaprilat in hypertensive emergencies.
The purpose of the study was to detect the safety and efficacy of enalaprilat in treatment of hypertensive emergencies with left ventricular (LV) failure.
46 patients with hypertensive crisis who had clinical signs of LV failure and pulmonary edema (35F:11M, mean age 53 yrs) were recruited. Among them 65.2% had chronic coronary artery disease, 13.0% had dilated cardiomyopathy. Initial mean systolic blood pressure (BP) levels were 234 mmHg, diastolic BP levels were 146 mmHg. Studied patients were randomly divided into group A (n=23, who received nitroglycerine i.v. + furosemide i.v.) and group B (n=23, who received enalaprilat i.v. + furosemide i.v.). In some cases due to partial inefficacy of basic antihypertensive treatment morphine and/or trimetaphan i.v. were also used. BP target in all the groups was typically 10-15% decrease of initial BP level; then we usually started oral medications.
Results: In A group during 6 hours after admission target BP was achieved in 82.6% of patients, although in 21.7% patients there was more substantial then desirable decrease of BP (BP failling). In B group during this period target BP was achieved in 86.9%, and only 4.3% of patients demonstrated nondesirable decrease of BP. There were no substantial differences between groups in the mentioned above parameters as well as in post-crisis follow-up.
Conclusion: Enalaprilat i.v. represents safe and effective medication in treatment of hypertensive emergencies complicated with LV failure.

P1157 Calcium channel activity as a predictor of the therapeutic effictiency of amlodipine in the treatment of essential hypertension

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The therapeutic effectiveness of amlodipine was studied in 25 patients with essential hypertension (EH) taking into account calcium channel activity in platelets. Methods of 24-hour blood pressure (BP) monitoring, two-dimension echocardiography were used, and basal and induced Ca^{2+} levels in platelets were determined using a fluorescent probe Fura – 2. As an inducer of the entry of calcium into platelets we used adenosine diphosphate (ADP) in a concentration of 10 mkM. Treatment with amlodipine (Norvask of the firm "Pfizer", USA) lasted 6 months, the daily dose was 5-10 mg. Depending on the effectiveness of the treatment all the EH patients were divided into 2 groups. The first group consisted of 18 patients in whom during long-term treatment with amlodipine average daily levels of mean BP decreased by 10 mm Hg and more. The second group included 7 patients in whom reduction of average daily levels of mean BP by the end of treatment was less than 10 mm Hg.
When calcium channel activity in the analyzed groups of patients was studied before treatment we found significant differences in the induction of Ca^{2+} entry into the cell in response to ADP. Thus, in group 1 EH patients the maximal increase of intracellular Ca^{2+} during stimulation by ADP was consistently greater than in group 2 patients (404,1±10,1 nM versus 238,5±16,6 nM, respectively), indicating calcium channel hyperactivity in these patients. Six-month therapy with amlodipine in group 1 EH patients led to a considerably lesser increase in the concentration of ADP-induced Ca^{2+} in platelets, indicating effective blockade of Ca^{2+} entry into the cells through ATP/ADP-dependent calcium channels by amlodipine. At the same time, in group 2 EH patients course treatment with this agent was not accompanied by a consistently lesser increase in the concentration of intracellular Ca^{2+} in platelets in response to stimulation by ADP. Basal concentration of intracellular Ca^{2+} remained unchanged in both groups after treatment with amlodipine.
Thus, administration of calcium antagonists in patients with calcium channel hyperactivity ensures effective blockade of Ca^{2+} entry into the cells, and this is accompanied by a stable hypotensive effect.

P1158 A population-based study of compliance and persistency with selected agents used in hypertension management

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Purpose: To conduct a head to head comparison of persistency and compliance associated with representative agents used in the pharmacologic management of hypertension including lisinopril (Zestril), valsartan (Diovan), amlodipine (Norvasc) in a usual care setting.
Methods: This retrospective database study utilized patients continuously benefit-eligible from the Merck-Medco pharmacy claims database from 8/1997 through 7/2000 (N=14.6M). Patients who received an initial (no prescription filled within class during prior 12 months) prescription for lisinopril, valsartan, or amlodipine between 8/1998 through 7/1999 (N=142,945) were included and followed for 12 months. Compliance was assessed using the medication possession ratio (MPR), or the percentage of time a patient had drug available over a 1-year time period. Patients were considered to remain "on therapy" until a therapy gap of >60 days occurred. To control for differences in overall baseline chronic disease burden, a Chronic Disease Score (CDS), which uses drug markers to identify chronic con-ditions, was used to classify the cohort as mild, moderate, or severe.
Results: Mean age of the study cohort was 63.1 years and 53% were female. Over half (51%) of the cohort used amlodipine as initial therapy, 21% valsartan, and 28% lisinopril. More valsartan patients remained persistent on therapy at 12-months post-therapy initiation (63%) compared to amlodipine (53%) and lisinopril (50%) ($p<.0001$, both comparisons). Mean duration of therapy was 266 days for valsartan patients versus 246 days for amlodipine and 240 days for lisinopril ($p<.0001$, both comparisons). Compliance was also greatest for valsartan patients, reflecting a mean MPR of 76% vs. 67% for amlodipine, 65% for lisinopril ($p<.0001$, both comparisons). While a slightly greater proportion of valsartan patients had a lower CDS (31% classified as severe, vs. 35% for both lisinopril and amlodipine), compliance and duration of therapy remained greater for valsartan patients across all CDS strata. Valsartan patients classified as severe via CDS had a mean duration of therapy of 266 days, compared to 245 for amlodipine and 237 for lisinopril ($p<.0001$, both comparisons). These patients also had a mean MPR of 75% as compared to 67% and 64% for amlodipine and lisinopril patients, respectively ($p<.0001$, both comparisons).
Conclusions: These preliminary results suggest that patients receiving valsartan in a typical managed care setting for the treatment of hypertension may be more adherent to therapy. These differences appear to be independent of baseline CDS.

P1159 Discontinuation, switching and adding among antihypertensive drug classes

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Medical and pharmacy claims from a database containing 2.5 million covered members were used to estimate discontinuation, switching, and adding rates for calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and beta-blockers (BB).
Continuously enrolled members (1/1/97 to 8/30/99) with at least one ICD-9 diagnosis code for hypertension, no claims for antihpertensive drug in 1997, and at least one claim for a CCB, ACEI, ARB and BB initially filled after 1997 were followed until end of study period (8/30/99). For all drug groups, discontinuation rates were estimated using non-parametric survival analysis. Switching patterns were assessed for patients who discontinued therapy and addition patterns were assessed for patients who did not discontinued therapy.
Patients identified in each drug classes were as follows: CCB 7,315; ACEI 6,882; ARB 2,018 and BB 5,829. Mean age of patients was similar between the drug classes (range 57-61). Most patients were females (range 52-55%) except for beta-blocker patients where 48% were females. The percentages of patients discontinuing therapy in each drug class were 51% (CCB), 50% (BB), 49% (ACEI), and 46% (ARB). Non-parametric survival estimates of time to discontinuation indicated slightly higher persistency at one year for ARB (44%) compared to ACEI and BB (42%) and CCB (40%). Almost 7% of patients who discontinued CCB switched to other antihypertensives (10.7% ACEI; 12.7% ARB and 7.7% BB).
Among patients who did not discontinue initial therapy, 25.2% of BB; 22% of CCB patients; 20.3% of ACEI patients; and 17.7% of ARB patients added another antihypertensive medication. Diuretics were the most commonly added medication for all drug groups (CCB 9.5%, ACEI 8.3%, ARB 7.3%, and BB 10.5%). In addition, ACEI therapy was added to 5.7% of CCB patients. For ACEI, ARB, and BB patients, 5-6% added CCB therapy.
In review of the drug classes, this analysis suggests that patients initiating ARB therapy have the highest persistency. Additionally, ARB has the lowest and BB has the highest rates of antihypertensive drug added to the regimen.

P1160 Angiotensin-converting enzyme inhibitor, but not beta blocker diminish the influence of gene polymorphisms of the renin-angiotensin system on blood pressure

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Background: Several gene polymorphisms (PM) of the renin-angiotensin-aldosteron system (RAAS) and of the endothelial NO-release are associated with the incidence of arterial hypertension (HT).
Objective: Influence of PM of the RAAS [angiotensinogen (ANG Thr174Meth, ANG Meth235Thr, ACE insertion/deletion (ID)] and the endothelial NO-system [eNos glu298asp (eNos298) and eNos T-786C PM (eNOS786)] on blood pressure (BP)
Methods: Analysis of stable consecutive pts with hypertension who underwent a coronary angiography due to clinical reasons. BP was measured invasively during heart catheter procedure at steady state.
Results: 1738 pts met inclusion criteria: HT (age 65±9, male 72%, CAD 77%, previous myocardial infarction 51%, smoking 35%, diabetes 41%, hypercholesterolemia 71%, treatment: beta blocker 73%, ace inhibitor 65%). All PM were in Hardy Weinberg equlibrium. In ANG 235 and eNOS786 PM there was no association with BP.

BP in pts without beta blocker and ACE inhibitor (n=102)

PM	ACE ID	ANG 174	eNOS298
	II/ID/DD	TT/TM/MM	GG/AG/AA
BP mean, mmHG	97/102/104*	100/106/115*	103/103/92*
BP systolic, mmHG	144/151/152	147/154/170*	151/151/129*
BP diastolic, mmHG	72/74/74	72/77/88*	74/74/69*

data are median; *p<0.05 for trend (Kruskal Wallis test)

In patients treated with beta blockers, Ang174, ACE ID, Ang235 PM showed again a stepwise increase of BP with the number of mutated alleles (p<0.05 for trend). In patients treated with ACE inhibitors alone or in combination with beta blockers, an association between the determined PM were not observed.
Conclusion: (1) Consenting with literature data, polymorphisms of RAAS and endothelial NO-system are associated with blood pressure levels in stable hypertensive patients.
(2) Chronic beta blockade alone does not alter the association of the PM of the RAAS on BP, while ACE inhibitors are able to suppress the effects of the PM on BP.

P1161 Very low-dose perindopril 2mg/indapamide 0.625mg reduces left ventricular hypertrophy in hypertensive patients

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Objective: The aim of this study is to compare the LVH regression over 12 month in hypertensive patients receiving Perindopril 2mg/Indapamide 0.625mg versus atenolol 50mg.
Methods: Ancillary, international (13 countries), double blind, randomized, controlled study with 2 parallel groups: Perindopril 2 mg/Indapamide 0.625mg combination (Per/Ind) or atenolol 50mg (ate). Out of the 471 randomised patients, 124 patients (59.7% men; age: 53.2±11.8 years; BMI: 26.9±2.9 kg/m^2) with essential systolic and diastolic or isolated systolic hypertension (160=<SBP<210mmHg and/or 95=<DBP<110mmHg) and with left ventricular hypertrophy confirmed by control echocardiography (defined by left ventricular mass index LVMI >100 g/m^2 for women, >120g/m^2 for men) are analysed. Doses could be adapted according to the BP level (1 or 2 tablets once daily).
Results: The echocardiography results (mean±sd) are summarized in the following table (PPS analyses).

Mean change (end - M0) of echo parameters

	Per/Ind (n=70)	ate (n=54)	P inter group
LVMI (g/m^2)	-11.3±15.4*	-5.3±15.1*	0.031
LVIDd (mm)	-0.9±2.1*	-0.2±1.9ns	0.017
IVSTd (mm)	-0.4±0.8*	-0.2±0.8ns	ns
PWTd (mm)	-0.6±0.8*	-0.2±0.7*	ns

p Fisher test adjusted on age sex and baseline; *p intra group <0.05; LVMI: left ventricular mass index caculated from LVM/BSA; LVIDd: diatolic left ventricular internal diameter; IVSTd: diastolic interventricular septal thickness; PWTd: diatolic posterior wall thickness

In this substudy the decrease (mean±sd mmHg) in brachial SBP, PP and DBP are respectively for Per/Ind: -22.7±14.0; -9.7±11.1; -13.0±6.9 and for ate: -17.6±18.4; -5.4±16.4; -12.2±9.8, (p=0.037; p=0.026; p=0.501). Similar results are observed in the echocardiography full analysis set (Per/Ind n=110, ate n=104): the decrease (mean±sd) in LVMI, LVIDd, IVSTd, PWTd are respectively for Per/Ind:-6.6±15.6;-0.6±2.0; -0.2±0.8;-0.3±0.8 and for ate:-2.1±14.5;-0.0±2.7;-0.1±0.8;-0.1±0.6,(p=0.032;p=0.016;p=0.869;p=0.245).
Conclusion: Very-low dose Perindopril/Indapamide combination shows a greater and significant decrease in LVH parameters than atenolol after one year of treatment.

P1162 Beneficial effects of nebivolol on the NO-pathway in essential hypertensive patients

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A number of experimental studies indicate that nebivolol interferes with the nitric oxide (NO) pathway. Essential hypertension (EH) is well known to be associated with endothelial dysfunction, a marker of future vascular atherosclerosis. The present study addresses the comparative effects of vasodilating beta-blocking agent nebivolol and atenolol on basal NO production during long-term treatment in essential hypertensive patients. 53 patients with EH were randomized to nebivolol 5 mg/day (n=25) and atenolol 100 mg/day (n=28) and treated for 24 weeks. The mean patients age was 55±8 yrs. Patients had no concomitant diseases and medication. Plasma and urinary nitrate concentrations were assessed in all EH patients at baseline (38±7 nmol/ml and 0.29±5 micromol/ml, respectively). Blood pressure reduction was achieved in both treatment arms and the drug antihypertensive action did not differ significantly. In nebivolol group plasma nitrate levels were significantly increased to 52±5 nmol/ml (p< 0.05 vs hypertensive patients at baseline), while in atenolol group this increment was nonsignificant (42±6, nmol/ml; p=0.837 vs hypertensive patients at baseline). Similarly, urinary nitrate concentrations were significantly increased to 0.59±0.12 micromol/ml (p< 0.01 vs hypertensive patients at baseline), while in atenolol group this increment was nonsignificant (0.32±0.13, micromol/ml; p=0.911 vs hypertensive patients at baseline). Our data indicate that in hypertensive patients nebivolol, but not atenolol, can produce a significant effect on basal NO production. These long-term beneficial effects on the NO-pathway can retard vascular dysfunction and atherogenesis in hypertensive patients.

P1163 Eplerenone is safe and effective as add-on therapy in hypertensive patients uncontrolled with calcium channel blockers or beta blockers

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In hypertensive patients who respond inadequately to monotherapy, JNC-VI recommends add-on therapy with a second drug of different MOA. This study examined whether the selective aldosterone blocker eplerenone (EPL) was safe and efficacious as add-on therapy in difficult-to-treat hypertensives uncontrolled on calcium channel blockers (CCBs) or beta-blockers (BBs).
In this 8-week, double-blind, multicenter study, 272 hypertensives whose blood pressure was not controlled with a CCB or a BB were randomized to receive 50 mg EPL once daily (uptitrating to 100 mg if required) or placebo (PBO). Study assessments included mean change from baseline in SBP/DBP, responder rates (DBP <90 mmHg or >=10 mmHg reduction from baseline DBP), AEs, and clinical laboratory values.
Within each cohort, there were no significant differences in heart rate, clinical laboratory values, and incidence of overall or specific treatment-emergent AEs between EPL and PBO. One patient in the BB plus EPL group withdrew due to a non-serious case of elevated K^+.

Efficacy at Week 8

	EPL	PBO	P-value
CCB cohort (1)	N=67	N=66	
Baseline SBP/DBP (mmHg)	154.2/98.9	157.6/99.4	
Change in SBP/DBP (mmHg	-17.2/-11.7	-10.5/-9.8	<0.001/0.101
Responder rate	71.6%	62.1%	0.204
Up-titration rate	43.3%	65.2%	
BB cohort (2)	N=69	N=66	
Baseline SBP/DBP (mmHg)	158.2/99.0	157.2/98.8	
Change in SBP/DBP (mmHg)	-19.1/-12.3	-11.0/-8.8	<0.001/0.008
Responder rate	75.4%	50%	0.002
Up-titration rate	39.1%	68.2%	

(1) Most common CCB: amlodipine (37.1% EPL, 41.8% PBO) and felodipine (20.0% EPL, 16.4% PBO).(2) Most common BB: bisoprolol (36.2% EPL, 34.8% PBO) and atenolol (29.0% EPL, 27.3% PBO).

In conclusion, addition of eplerenone further reduced blood pressure and increased responder rates in this difficult-to-treat population uncontrolled on CCBs or BBs. Aldosterone receptor blockade with eplerenone provides incremental blood pressure lowering on top of CCB or BB and is rational add-on therapy in uncontrolled hypertensive patients.

P1164 Case-control investigation into the risk factors of the undesirable effects of antihypertensive treatments in general medicine

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Objectives: to look into the existence of specific clinical profiles in patients presenting with undesirable effects during antihypertensive treatments.
Methods and Material: Epidemiological case-control investigation. The cases were patients with treated hypertension presenting with any kind of undesirable effect. The controls were the first two patients with treated hypertension consulting a doctor during the same period and not presenting with any undesirable effect.
Results: 3031 patients aged 63 ± 11 years took part in the investigation, among whom 37.9% (n=1149) presented with a secondary effect which justified a modification in their antihypertensive treatment. The controls and cases were comparable in terms of age, sex, length of time they had suffered from hypertension, tension parameters, the existence of a cardiovascular history. They differed in terms of the conditions of discovery (5.9% vs 8.4% for occupational medicine: $p<0.05$), the frequency of occurrence of undesirable effects from antihypertensive medication (8.2% vs 19.0%: $p<0.001$) or from other medication (14.5% vs 19.8%: $p<0.001$), the existence of a known allergic condition (4.5% vs 8.6%: $p<0.001$), a history of acute allergic reactions (8.9% vs 12.0%: $p<0.01$), the existence of a condition which could induce allergy (7.5% vs 10.4%: $p<0.01$); the extent of treatment compliance (80.8% vs 76.2%: $p<0.05$) and the number of medication (more than 5: 9.5 vs 15.4%: $p<0.001$). All of these factors, significant in univariate analysis, were introduced into a multivariate model of logistic regression. Its results showed a common profile among patients presenting with undesirable effects during antihypertensive treatment characterized by the existence of a history of undesirable effects from antihypertension medication ($p<0.001$) or others ($p<0.01$), of chronic allergies ($p<0.01$), a large number of medication ($p<0.01$), and the lack of compliance of the patient with his/her treatment ($p<0.01$).
Conclusion: An undesirable effect occurs within a framework of three possible dimensions, a chemical dimension, linked with the number of possible interactions between medication, an allergic dimension, and a psychological dimension, influenced by the conditions of discovery of the hypertension and the compliance of the patient with his or her treatment. A predictive score is now being studied on the basis of these results.

P1165 Efficacy and safety of sildenafil citrate in men with erectile dysfunction who are taking multiple antihypertensives

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Erectile dysfunction (ED) is common in men taking antihypertensive agents (anti-HTNs). We evaluated the efficacy and safety of sildenafil citrate in men with ED taking >=2 anti-HTNs. 568 men with ED taking >=2 anti-HTNs were randomized to sildenafil (50 mg, flexible) or placebo for a 6-week, double-blind (DB) phase followed by a 6-week, open-label (OL) extension. Primary efficacy variables were questions 3 (Q3; achieve erection) and 4 (Q4; maintain erection) of the International Index of Erectile Function. Patients completing DB were eligible for OL. Adverse events (AEs) and causality were recorded. 562 men (mean age 59.3 years) received study drug. The mean duration of ED was 4.5 years; the mean duration of HTN was 11.7 years. For analytic purposes, patients were divided into men taking 2 anti-HTNs (n=324) and those taking 3+ anti-HTNs (n=235). Results were similar in men taking 2 or 3+ anti-HTNs. At week 6, scores on Q3 and Q4 improved significantly from baseline in sildenafil- versus placebo-treated patients. 62% of intercourse attempts were successful in the sildenafil group vs 26% in the placebo group. After OL, >80% of patients who received DB sildenafil or placebo reported improved erections and intercourse. Intercourse success rates in the 2 groups were identical (71%). At week 6, 40% of sildenafil- and 26% of placebo-treated patients experienced AEs; 3 (1.9%) sildenafil- and 2 (1.4%) placebo-treated patients discontinued due to treatment-related AEs. Two other patients (0.7%) from each group had serious adverse events (SAEs); none were treatment-related. AEs associated with changes in blood pressure were (sildenafil vs placebo): hypotension (0.7% vs 0%), postural hypotension (0.4% vs 0.4%), and dizziness (2% vs 2%). During OL, 3 DB placebo patients (1.9%) discontinued due to treatment-related AEs. There were no SAEs related to changes in blood pressure. These results suggest that sildenafil is an effective and well-tolerated treatment for ED in men taking 2 or more anti-HTNs.

P1166 Selective aldosterone blockade with eplerenone regresses ventricular mass in patients with left ventricular hypertrophy

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High levels of aldosterone correlate with left ventricular hypertrophy (LVH) and mediate an inflammatory response in animals that may result in myocardial fibrosis. This study examined whether aldosterone antagonism with eplerenone (EPL), the selective aldosterone blocker, reduced LV mass compared to enalapril (ENAL) and EPL/ENAL combination therapy.
In this 9-month, double-blind, forced-titration study, patients with LVH and hypertension (DBP ≥90 mmHg and <114 mmHg; SBP >140 mmHg and ≤200 mmHg) were randomized to receive once-daily EPL 200 mg, enalapril (ENAL) 40 mg, or EPL 200 mg/ENAL 10 mg (doses reached by forced titration over 4 weeks). The primary endpoint was change in LV mass (LVM) as assessed by MRI. To limit hypertension as a confounding variable, HCTZ 12.5, HCTZ 25 mg, or amlodipine (AML) 10 mg were added at Week 8 if BP remained uncontrolled. SBP/DBP, urinary albumin:creatinine ratio (UACR), and safety were also assessed at Month 9 (see table, p. 212).
Add-on HCTZ or AML was required by 30%, 59%, and 20% of patients receiving EPL, ENAL and EPL/ENAL, respectively. A significantly greater proportion of ENAL patients experienced coughing than EPL patients (14.1% vs 3.1%, P=0.033).
Selective aldosterone blockade with eplerenone was as effective as enalapril in regressing LVH. The combination of eplerenone and enalapril conferred cardiovascular benefits additive with an ACE inhibitor.

Abstract P1166 – Table: Change in LVM, BP, and UACR

	EPL (N=50)	ENAL (N=54)	EPL+ENAL (N=49)
LVM			
Mean baseline LVM [g (SD)]	189.9 (53.9)	188.5 (51.7)	192.8 (61.4)
Adjusted mean change [g (SE)]	-14.5 (3.36)	-19.7 (3.20)	-27.2 (3.39)
P-values vs ENAL	0.258		
P-values vs EPL/ENAL	0.007	0.107	
SBP/DBP			
Mean baseline SBP/DBP [mmHg]	163.2/97.4	163.7/98.9	162.9/98.5
Adjusted mean change [mmHg (SE)]	-23.8/-11.9(1.78/1.02)	-24.7/-13.4(1.69/0.97)	-28.7/-14.4(1.79/1.03)
P-values vs ENAL	0.718/0.269		
P-values vs EPL/ENAL	0.048/0.076	0.098/0.480	
Change in UACR from baseline (%)*	-24.9%	-37.4%	-52.6%
P-values vs EPL/ENAL	0.001	0.038	

*All treatments significantly reduced UACR from baseline

P1167 Effects of adding an aldosterone receptor antagonist to an angiotensin converting enzyme inhibitor in patients with hypertension

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Background: Hypertensive patients (pts) have been shown to have abnormal endothelium-dependent vasodilatation (EDVD). Considering that either angiotensin II or aldosterone has been implicated in determining endothelial dysfunction in experimental hypertension, we hypothesised a positive interaction between aldosterone receptor antagonist (ARA) and angiotensin converting enzyme inhibitor (ACE-I) in improving endothelial function.
Methods: We examined 52 pts [57.6% females (n=30); age 62 ± 8] with mild-moderate hypertension. Pts with diabetes mellitus, hyperlipidemia, smoking habits were excluded. Among the enrolled pts, 25 (48%) (group 1) were randomly assigned to the treatment with an ACE-I (lisinipril 20 mg/die), and 27 (52%) (group 2) to a combined treatment with lisinopril (20 mg/die) plus low-dose of an ARA (potassium kanrenoate, 50 mg/die). EDVD was assessed at baseline and after 6 months of treatment. It was evaluated by measuring the diameter of the brachial artery (ultrasound method) before and during reactive hyperaemia (induced after deflation of a blood pressure cuff inflated to suprasystolic pressure for 5 minutes) and was calculated from the diameters as: (reactive hyperemia - baseline)/baseline X 100%.
Results: After 6 months of treatment, we noticed a significant decrease in mean blood pressure and a significant increase in EDVD in the two groups respect to baseline. EDVD was significantly less in the lisinopril treated group (group 1) than in the lisinopril plus potassium kanrenoate treated group (group 2) (Table)

	baseline	6 months
Mean blood pressure, mmHg		
ACE-I treated group	115.3 ± 9.9	100.2 ± 9.6 *
ACE-I plus ARA treated group	115.2 ± 9.5	98.9 ± 9.3 *
intergroup comparison	p < ns	p < ns
Endothelial dependent vasodilation, %		
ACE-I treated group	6.4 ± 3.6	9.2 ± 4.1 *
ACE-i plus ARA treated group	6.5 ± 4.3	14.5 ± 5.1 **
intergroup comparison	p < ns	p < 0.01

* p < 0.01 versus group 1; ** p < 0.001 versus group 1

Conclusions: low-dose of an ARA added to an ACE-I leading to marked effects on endothelial function that were less apparent by treatment with ACE-I alone.

P1168 Effect of antihypertensive therapy on arterial distensibility in older patients

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Arterial compliance decline substantially with age. In older patients (pt) the effect of antihypertensive therapy on the arterial stiffness should be taken into account. In this regard antihypertensive drugs have unequal efficacy.
The aim of this study was to assess the ability of three different antihypertensive regimens to improve arterial distensibility. There were included 85 pt, with similar basal characteristics, mean age 72±12 yrs, with mild to severe hypertension. Secondary hypertension, complicated hypertension with severe organ damage and concurrent severe illness requiring sustained medication were exclusion criteria. The pt. were randomly assigned to one of the three therapy groups: felodipine (5mg qd, group F), perindopril (4mg qd, group P) and losartan (25mg bid, group L). The dosage was increased to10mg qd in group F, 8mg qd in group P and 50mg bid in group L and/or a diuretic was added in order to achieve a target blood pressure (BP) < 140/90 mmHg. The evaluation of drug efficacy was performed monthly during the first 3 month and at the end of the follow-up period of 11±3 months (FU). BP was measured according WHO guidelines and an average of three measurements was analyzed. Aortic distensibilty (AD, 10^{-3} mmHg^{-1}) was determined at baseline and at FU. The AD was defined as the difference between end-systolic and end-diastolic aortic area divided by the product of brachial pulse pressure (PP) and end-diastolic aortic area. Aortic area was determined by echocardiography at 4 cm above aortic valves.
After the FU period the systolic BP decreased significantly in all groups (-6±14mmHg in group F, -23±17mmHg in group P, -24±16 in group L, p<0.01), without significant differences between groups. Diastolic BP also decreased significantly (-21±13mmHg in group F, -13± 9mmHg in group P and -14±10mmHg in group L) but more in group F (p<0.05). PP decreased significantly only in group P and L (p<0.01 vs. basal, p<0.05 vs. F, p:NS P vs. L). AD increased significantly in group P and L (1.1± 0.1 in group P, 1.5± 0.3 in group L, p<0.01 vs. basal, p<0.05 L vs. P) but not in group F.
Conclusion: felodipine, perindopril and losartan are equally effective antihypertensive drugs in elderly pt. However, the efficacy on the arterial wall seems to be better for perindopril and losartan. This effect could be mediated through a decrease in PP and possibly through a direct arterial wall effect for losartan.

P1169 Effects of pravastatin on blood pressure and vascular reactivity in hypercholesterolemic patients with borderline hypertension

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Objective: Increasing data have shown that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) possess vascular protective actions beyond their primary cholesterol-lowering effects. The present study was designed to investigate the effects of two different doses of pravastatin and a low salt diet on resting and stimulated blood pressure (BP), peripheral vascular hemodynamic and lipid profile in hypercholesterolemic patients with borderline hypertension (HC-BHT).
Design and Methods. Nineteen untreated young (age 33.5±5.5 year) HC-BHT subjects with average office BP=145/88 mmHg were studied at baseline (B), 4 weeks after a low salt diet (LS, NaCl 50-75 mEq/day) and 8 weeks after a single-blind, randomized treatment with pravastatin 20 or 40 mg/day (P). Each patient underwent the following determination: office and 24-hour ambulatory systolic and diastolic BP, forearm blood flow (FBF) and vascular resistance (FVR) by venous occlusion plethysmography, mental arithmetic (MA) and hand grip (HG) test, and serum cholesterol (T-Chol, HDL and LDL) levels.
Results: Pravastatin reduced both systolic and diastolic BP in comparison to B and LS both during day-time and night-time (average 24-hour BP: B=137/88, LS=136/88, P=131/82 mmHg; p<0.001 P vs. B, LS). The average 24-hour BP reduction was enhanced in patients treated with the higher dose of P (40 mg/day 136/87 vs. 127/78 mmHg, p<0.01; 20 mg/day 137/88 vs. 133/84 mmHg, p<0.05). Pravastatin also blunted the pressor response to MA and HG, increased FBF (B=3.4, LS=4.1, P=5.4 ml/min/100 ml; p<0.01 P vs. LS) and reduced FVR (B=29, LS=23, P=19 units; p<0.01 P vs. LS) in comparison to LS diet and again the changes were enhanced in patients treated with the higher dose. Serum cholesterol levels were reduced by P even whether the changes were only weakly and not significantly related to BP modifications observed both at rest (Delta DBP Casual/Delta T-Chol, R2=0.02, p=0.647) and in response to MA (Delta DBP MA/Delta T-Chol, R2=0.26, p=0.285) and HG (Delta DBP HG/Delta T-Chol R2=0.09, p=0.304).
Conclusions: These data suggest that statins can significantly improve BP control in patients with BHT both at rest and in response to various stressful stimulations. Moreover, BP decline was associated with an enhancement of the peripheral vasodilator capacity that could contribute to improve BP control. In particular, the effects of pravastatin seem to be dose-related and only weakly related to serum cholesterol changes suggesting a direct effect of the drug on peripheral vascular tone in patients with BHT.

P1170 Benefit of a treatment strategy based on a very low dose combination of perindopril and Indapamide in albuminuric hypertensive type 2 diabetics

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The objective is to compare the beneficial effect of treatment based on the very low dose combination Perindopril 2mg/Indapamide 0.625mg (Per/Ind) vs Enalapril (Ena) on albuminuria excretion rate (AER) regression in hypertensive type 2 diabetics.

The design was a 12-month, randomised, double-blind, parallel group study. AER was evaluated on overnight urine collections in central laboratory. Albuminuric (20<=AER<500µg/min) hypertensive (140mmHg<=SBP<180mmHg and DBP<110mmHg) type 2 diabetics (well-controlled: HbA1c<9%) were randomised to Per/Ind or to Ena od. A dose titration by doubling the dosage in 3 steps, from Per 2/Ind 0.625mg to Per 8/Ind 2.5mg or Ena 10mg to 40mg was permitted after W12. Statistical analysis was carried out on the log transformed values using a Student's- t test after adjustment on the baseline and country, alpha=2.5%. 481 patients were randomised: 59.1±8.7 years, 61% male.

Results from 457 patients (ITT) have shown a significant higher reduction of AER in Per/Ind group -42% [-50%;-33%] compared with Ena group -27% [-37%;-16%](p=0.002).

Both treatments reduced BP. A statistical significant higher decrease in SBP(-3.01mmHg) and DBP (-1.54mmHg) was observed in the Per/Ind group. Therefore, the higher reduction in AER remained significant after adjustment on final mean BP (MBP) (p=0.007). For each quartiles of final MBP, the residual AER were always lower with the Per/Ind than with Ena: see Table 1.

Table 1: Final AER according to final MBP

Quartiles of MBP (mmHg)	<98.9	[98.9;103.8[	[103.8;110.9[	>=110.9
Per/Ind (N=227)*	n=68	n=57	n=54	n=48
AER(µg/min)** 95%CI	40.3 [30.6;53.0]	45.4 [34.0;60.6]	42.6 [29.6;61.4]	51.5 [35.7;74.2]
Ena (N=222)*	n=57	n=45	n=56	n=64
AER(µg/min)** 95%CI	60.9 [42.3;87.8]	51.9 [34.2;78.5]	57.9 [40.4;82.9]	86.1 [63.2;117.3]

*missing values:6 for Per/Ind, 2 for Ena; **AER: Geometric mean

The frequency of adverse events was similar in the two groups. Incidence of emergent dyskaliemia <3.4mmol/l was 2.5% for Per/Ind vs 1.7% for Ena and >5.5mmol/l was respectively 3.3% vs 5.5%.

A treatment strategy based on a first line very low dose combination Per 2mg/Ind 0.625mg induces a greater decrease in albuminuria than Ena. The beneficial effect of the combination may not be explained by BP control alone and a possible synergistic effect between ACEI Perindopril and diuretic Indapamide may increase target organ protection through pharmacospecific effects.

P1171 Effects of losartan and enalapril at hypotensive and non-hypotensive doses on cardiac and renal interstitial matrix in hypertensive rats

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Hypertension is associated to abnormal accumulation of extracellular matrix in the heart and in the kidney. Angiotensin II and bradykinin may be involved, respectively, in the control of extracellular collagen synthesis and degradation. Thus, ACE inhibitors and angiotensin II type 1 receptor blockers (ARB) may have some effect on cardiac and glomerular extracellular matrix.

Objective: To evaluate the effects of an ACE inhibitor, enalapril (ENA) and of an ARB, losartan (LOS), administered either at hypotensive or non-hypotensive dosage, on the cardiac and renal interstitial matrix of spontaneously hypertensive rats (SHR).

Methods: One hundred rats were included in the study: 16 SHR were treated with low-dose (ld, 1mg/Kg/day) ENA, 16 with low-dose (ld, 0.5 mg/Kg/day) LOS, 16 with high-dose (hd, 25 mg/Kg/day) ENA, 16 with high-dose (hd, 15 mg/Kg/day) LOS, while 18 WKY and 18 SHR were kept untreated (unt). Treatment was given from the 4th to the 12th week of age. Systolic blood pressure (SBP) was measured non-invasively every week. The left ventricular weight to body weight (RLVM) and the left + right kidney weight to body weight (RKW) were measured, and the cardiac and glomerular collagen content was evaluated using Sirius red staining and image analysis.

Results: BP was significantly reduced in SHR ENA hd and in SHR LOS hd, while no reduction was observed in SHR ENA ld and SHR LOS ld. A significant reduction in RLVM was observed in SHR ENA hd and SHR LOS hd. The cardiac collagen was significantly reduced in SHR ENA hd and SHR LOS hd as well as in SHR LOS ld. No significant differences in RKW was observed between groups. However, the collagen content in the glomerular perivascular space was significantly reduced in all treated groups.

	SBP (mm Hg)	RLVM (g/Kg)	Cardiac collagen (%)	RKW (g/Kg)	Renal collagen (units)
WKY unt	157±16 ***	2.42±0.33 ***	3.3±0.6 ***	6.75±0.60	1792±800 ***
SHR unt	216±25	2.64±0.11	8.20±0.32	6.76±0.38	5724±225
SHR ENA ld	218±18	2.54±0.14	8.25±2.0	6.54±0.35	2524±464 ***
SHR LOS ld	216±18	2.61±0.15	5.11±0.26 ***	6.73±0.42	1922±777 ***
SHR ENA hd	157±16 ***#	2.15±0.14 ***	6.54±0.29 ***	6.70±0.33	1565±304 ***
SHR LOS hd	184±18 ***	2.23±0.13 ***	4.02±0.48 ***	6.84±0.38	1248±67 ***

***p<0.001 vs. SHR unt; #=p<0.001 vs. LOS hd

Conclusions: LOS and ENA may have different effects on the interstitial matrix in different organs.

P1172 Health care resource utilization among patients starting ACEI and ARB therapy

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Medical and pharmacy claims from a database containing more than 2.5 million covered lives were examined to evaluate the costs of outpatient laboratory and physician visits, hospitalizations, and ER visits among patients initiating angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), ACEI-diuretic combination, and ARB-diuretic combination.

Continuously enrolled members (1/1/97 to 8/30/99) with at least one ICD-9 diagnosis code for hypertension, no claims for antihpertensive drug in 1997, and at least one claim for an ACEI, ACEI-diuretic, ARB, ARB-diuretic therapy filled between Jan 1, 1998 and August 30, 1998 were followed for 12 months after initial prescription fill. Patient demographics, cardiovascular comorbid conditions and costs of health care utilization (outpatient laboratory and physician visits, hospitalizations, and ER visits) were assessed.

There were 3,725 ACEI patients, 426 ACEI-diuretic patients, 1,112 ARB patients, and 302 ARB-diuretic patients identified. The average age of patients in all groups was similar (57-59). The majority of patients starting ACEI and ARB were males (51% and 56%, respectively). Patients starting ACEI-diuretic and ARB-diuretic were mainly females (56% and 53%, respectively). Except for diabetes, baseline cardiovascular comorbid conditions were similar for all drug classes. Diabetes (17.4%) was more prevalent with ACEI patients than were ARB patients (10.8%) and similarly, for ACEI-diuretic (12.2%) and ARB-diuretic (5.6%) patients. The average annual total costs of health care utilization per patient were $2,551 for ACEI versus $2,329 for ARB and $1,665 for ACEI-diuretic versus $1,411 for ARB-diuretic. Lower cardiovascular and non-cardiovascular hospitalizations contributed to the lower total health care costs associated with ARB therapy. When averaged over all groups, hospitalization accounted for 71.8%; outpatient physician visits accounted for 21.3%; ER visits accounted for 2.4%; and outpatient laboratory accounted for 4.5% of the total costs.

This analysis suggests that patients initiating ARB therapy had lower total health care resource utilization costs one year following initiation of therapy.

MYOCARDIAL ISCHAEMIA – EXPERIMENTAL STUDIES

P1173 Remote preconditioning protects the heart by activating myocardial PKCepsilon-isoform

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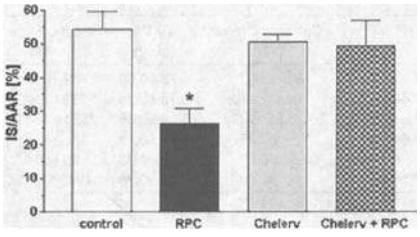
Myocardial protection can be achieved by brief ischemia-reperfusion of remote organs, a phenomenon described as remote preconditioning (RPC). Since the intracellular mechanisms of RPC are not known, we tested the hypothesis that RPC might activate myo-cardial PKCepsilon - an essential mediator of classical ischemic preconditioning. Furthermore, we tried to delineate the mechanisms by which RPC is transduced to the heart with respect to the possible contribution of kinins and neuronal reflexes.

Methods: Anesthetized rats were ran-domized to undergo either 30min of waiting (controls) or RPC (brief mesenteric artery occlusion followed by reperfusion) in the absence or presence of chelerythrine (5mg/kg), a specific PKC inhibitor. Myocardial infarct size was measured by TTC staining after 60 min of coronary artery occlusion followed by 150 min of reperfusion. In separate sets of experiments RPC was performed with or without pretreatment with HOE140, a selective B2-antagonist or hexamethonium was used to explore the influence of ganglion blockade on RPC. Translocation of PKCepsilon from cytosol to the particulate fraction was measured by quantitative im-munoblotting.

Results: RPC significantly reduced infarct size which was completely blocked by PKC inhibition. RPC shifted the ratio between cytosolic and particulate PKCe, an indica-tor for PKC-activation, from 0.95±0.06 in controls to 0.41±0.09 ($p<0.05$), and this effect was abolished by HOE140. Activation of PKCepsilon could not be achieved after pretreatment with HEX (0.69±0.06 in HEX vs. 0.78±0.06 in HEX+RPC).



RPC and PKC.

Conclusions: RPC activates myocardial PKCepsilon through a neuronal and bradykinin-dependent pathway. We assume that activation of PKCepsilon is an important step in cardioprotection induced by remote preconditioning.

P1174 Acute reduction of myocardial infarct size by a HMG-CoA reductase inhibitor is mediated by endothelial nitric oxide synthase

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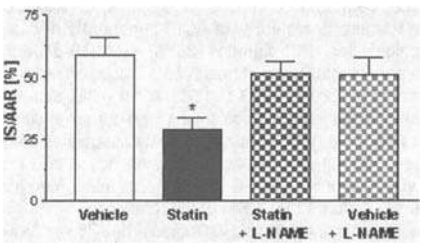
Background: In addition to their lipid lowering properties, statins improve endothelial function by increasing the activity of endothelial nitric oxide synthase (eNOS). By this mechanism, we hypothesized that statins may protect the myocardium from ischemic injury.

Methods: Anaesthetised rats underwent 30 min of coronary artery occlusion (CAO) followed by 180 min of reperfusion. Heart rate and arterial blood pressure were continuously monitored throughout the experiments. Plasma cholesterol concentrations were determined at the end of the experiments. Infarct size was measured by TTC staining and expressed as percentage of area at risk. Myocardial eNOS activity was measured by arginine to citrulline conversion assay. The rats were pretreated for one week either with cerivastatin (0.3 mg/kg/d) or placebo. In one set of experiments L-NAME (15 mg/kg), an inhibitor of eNOS, was applicated 15 min prior to CAO.

Results: Cerivastatin increased myocardial eNOS activity by 58% (12 ± 1 to 19 ± 2 pmol/mg/min, $P<0.05$) and decreased infarct size by 49% (59 ± 7% to 29 ± 5%) without affecting hemodynamics or plasma cholesterol levels. Cardioprotection and upregulation of eNOS activity were absent in rats co-treated with L-NAME.

Conclusion: Statins reduce the extent of myocardial necrosis after acute ischemia/reperfusion injury by increasing myocardial eNOS activity. Therefore, statins may protect the heart not only by reducing the incidence of ischemic events, but also by limiting cell damage during acute myocardial infarction.



Infarct size reduction by statins.

P1175 The development of an experimental closed chest animal model which simulates the clinical spectrum of chronic regional ischaemic myocardium

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There remains a need to establish a closed-chest, closed pericardium, non-collateralised animal model to mimic the varying clinical substrates associated with chronic regional ischemia.

Methods: A chronic porcine model was developed in which either a non-transmural (NTMI) or transmural (TMI) infarct or ischemia could be created by producing progressive intimal proliferation by implanting a copper-coated steal stent. Different stent coating protocols were tested. In Group 1 stents were electroplated for 120 seconds at 100mA current. Group 2 (less coated)-60 seconds at 100 mA. Group 3 (more coated)-60 seconds @100 mA plus 30 seconds at 150mA. In 32 pigs (Group 1-7 pigs, Group 2-18 pigs, Group 3-7 pigs), stents were implanted in the proximal Cx artery. All received aspirin and clopidogrel to prevent acute stent thrombosis. Weekly ultrasound studies were performed to monitor LV function. After 4-6 weeks, ultrasound Strain/Strain Rate, angiographic, Positron Emission Tomographic (PET), histopathologic and vessel morphometric data were compared (table).

Echo, histologic and angiographic data

	Normal Group (n=8)	NTMI Group (n=14)	TMI Group (n=4)
Wall-thickness (mm)	5.1 ± 0.1*	4.6 ± 0.4	3.5 ± 0.5
LV Diameter (mm)	37 ± 0.8*	42 ± 1.5	50 ± 2.1
Stenosis LCx (%)	0 ± 0 * #	93 ± 3	99 ± 1
Scar extension (%)	0 ± 0 * #	62 ± 8 *	100 ± 0

LV=left ventricle, LCx=left circumflex artery,*$p<0.05$ vs Transmural Infarction Group, #<0.05 vs Nontransmural Infarction Group

Results: Group 1: 4 pigs died during week one due to MI and 3 pigs progressed to severe stenosis (SS, >95%). Since this protocol was too aggressive it was stopped. Group 2: 4 pigs died from TMI during week one, 11 developed SS and 3 non-severe stenosis (NSS). In Group 3: 1 died from early MI, 2 developed SS and 4 survived TMI. The 4 pigs with TMI (occluded stents after 4 weeks) showed poor collateralisation on angio at 8 weeks. Quantitative coronary angiographic analysis was correlated to stent morphometry. Hibernating or infarcted myocardium was correctly identified in the "at risk area" by ultrasound findings and confirmed by PET and histology.

Conclusion: By varying the amount of copper deposited on the stent, it was possible to bias the resultant ischemic substrate to either NS (Group 2: 14%), SS (Group 2: 61%) or NTMI (Group 3: 57%) with a low mortality of 20% (Group 2+3).

P1176 The influence of PK-C inhibition, alfa adrenoreceptors antagonist and endocardial endothelium damage on heart contractility in hypoxic conditions

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Aim: the aim of present work was to examine the effects of 4-N-benzoyl staurospirine (CGP 41251 - inhibitor of alfa, beta protein kinase C isomers) on the rat isolated heart contractility under normoxic and hipoxic conditions. Additionally the effects of CGP 41251, alfa1a-adrenoreceptor antagonist (WB-4101), alfa1b adrenoreceptor antagonist (CEC - chloroethylclonidine) and selective damage of endothelium on the protection against hypoxia induced by ischemic preconditioning were examined. Materials and methods: the experiments were performed on rat isolated left ventricular papillary muscle mounted in organ bath. Force of contraction (Fc), velocity of relaxation (+dF/dt) and velocity of relaxation (-dF/dt) were measured. Isolated heart tissue was perfused with modified Krebs-Henseleit solution gassed with 95%O2; the temperature of perfusate was 37±0,5C. The papillary muscle was paced using two silver electrodes with frequency of 0,5Hz. Hypoxia was achieved by perfusion of tissue with substrate free solution gassed with 95%N2 for 60 min. Preconditioning was achieved by perfusion of tissue with substrate free solution, gassed with 95%N2 and pacing 1Hz for 10 min followed by 10 minutes of reperfusion. Results: At concentrations less than 1μM CGP 41251 did not cause any changes in contractility of rat heart. At concentration 3μM was observed significant positive inotropic effect (Fc 0,5±0,14mN in control vs 0,71±0,1mN, $p<0,05$). Pretreatment of papillary muscle by CGP 41251 at 3μM reduced decreasing of contractility by stimulated hypoxia and reperfusion (Fc 32% of control after hypoxia/reperfusion in control vs 59%, $p<0,05$). Preconditioning was not affected by addition of CGP 41251 neither 1 nor 3Mμ on Fc but velocity of relaxation (-dF/dt) was higher in group treated with CGP 41251 (1,4±0,04 vs 2,5±0,4 mN/s, $p<0,01$). Pretreatment with CEC at 3μM (Fc 84% of control vs 32% in CEC group, $p<0,01$) and selective damage of endocardial endothelium induced by fast immersion of papillary muscle in 0,5% Triton X-100 (Fc 84% of control vs 38% in Triton group, $p<0,01$), but not pretreatment with WB-4101 abolished the protective effects of preconditioning. Conclusions: The results imply that PK-C inhibition improves contractility of heart under normoxic and hypoxic conditions and does not alter hypoxic preconditioning in rat papillary muscle. Selective damage of endocardial endothelium prevented the protection of preconditioning against hypoxia/reperfusion injury. Alfa 1b adrenoreceptors and endocardial endothelium are both involved in triggering of preconditioning in rat isolated heart muscle.

P1177 The role of oxidative stress in alteration of Na-K ATPase isoform expession in rat heart during ischaemia-reperfusion

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The aim of this study was to assess (a) whether depression of cardiac performance and Na-K ATPase activity during ischemia and reperfusion is associated with alteration in Na-K ATPase isoform expression and (b) whether oxidative stress participates in this alteration. Cardiac performance, enzyme activity, isoform protein content as well as gene expression were studied in isolated rat hearts subjected to global ischemia alone (30 min) and global ischemia followed by reperfusion (60 min) in the presence or absence of superoxide dismutase plus catalase (SOD+CAT), a potent scavenger of oxyradicals. The effect of ischemia and reperfusion was compared to infusion with H2O2 or xanthine plus xanthine oxidase (XXO). Attenuation of cardiac performance and Na-K ATPase activity during ischemia and reperfusion was similar to that induced by H2O2 or XXO. Ischemia and reperfusion caused significant reduction of all alpha and beta isoform protein content, however, while alpha 2, alpha 3, beta 1, beta 2, and beta 3 were preserved by SOD+CAT, alpha 1 was reduced only slightly by ischemia and reperfusion and this decrease was not prevented by antioxidant treatment. H2O2 and XXO also depressed all isoforms but alpha 1. Similarly, mRNA level of alpha 1 was less affected than the other isoforms and was not protected by SOD+CAT. These results indicate that ischemia and reperfusion cause alteration in Na-K ATPase isoform expression and that oxidative stress plays a role in this alteration. Antioxidant treatment improves expression of all isoforms except alpha 1, which appears to be more resistant to oxidative stress.

P1178 Reduction of myocardial infarct size by a novel indole derivative with antioxidant and free radical scavenging properties

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Reactive oxygen species are involved in ischemia (isc)-reperfusion (rep) injury. The aim of this study was to investigate: a) the antioxidant properties of 3-[(1H)-indolylmethyl-4-amino 4,5-dihydro-H,1,2,4 triazolo thione] (C6458) in vitro, b) the protective ability of this compound against the oxidative damage of the heart after isc-rep in vivo and c) the potential efficacy of C6458 on the reduction of the infarct size (IS) in vivo. Methods: The ability of C6458 to scavenge free radicals was tested by the interaction with the 1,1-diphenyl-2-picrylhydrazyl (DPPH) stable free radical and by the competition with DMSO for OH. The protective ability of C6458 against oxidative damage after isc-rep was examined in male rabbits that were subjected to 30 min regional isc and 120 min of rep. C6458 was continuously infused for 30 min starting at the 10th min of isc and ending at the 10th min of rep at 2 doses (100 μM and 200 μM). The antioxidant activity was detected by the measurement of malondialdehyde (MDA) formation and the IS was assessed. Results: C6458 showed significant antioxidant properties in all the above assays in vitro; it also exerted significant antioxidant activity in vivo and protected against oxidative damage during isc -rep in both doses. The levels of MDA produced by C6458 at the dose of 200 μM were significantly lower from the 1st min of rep compared to the controls, while at 100 μM this reduction was observed at the 20th min of rep. 200 μM/Kg of C6458 reduced significantly the IS from 45.4±5.4% to 27.3±3.3% ($P<0.05$ vs Control). Conclusion: The novel antioxidant agent C6458 is protective against the oxidative damage of the myocardium after isc-rep and reduces IS. This beneficial effect may be related to its antioxidant and free radical scavenging activity.

P1179 Endothelin-A receptor antagonist LU 135 252 has no electrophysiological and antiarrhythmic effects during myocardial ischaemia-reperfusion in dogs

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Antiarrhythmic role of endothelin-A receptor antagonists during myocardial ischemia and reperfusion remains controversial. Moreover electrophysiological mechanism has not yet been identified. The aim of the study was to investigate the role of endogenous endothelin-1 (ET-1) in the development of ventricular tachyarrhythmias during myocardial ischemia and reperfusion using endothelin-A receptor antagonist LU 135 252 (LU) in a canine model. LU (1mg/kg, n=10) or saline (control, n=10) bolus was injected intracoronary into the left anterior descending coronary artery (LAD) before the onset of ligation of this vessel for 30 minutes followed by a 90-minute reperfusion period. Left and right ventricular monophasic action potentials (MAP) were registrated. Serum ET-1 and big-endothelin levels were determined from coronary sinus. Results: There was no difference in hemodynamical parameters and in the left ventricular ischemic mass between the two groups. Total incidence of ventricular fibrillation (VF) during ischemia and reperfusion was 40% in control and 50% in LU group (NS). There was no significant difference in the incidence of sustained tachycardias (VT) and nonsustained VT-s and in the number of ventricular premature beats between the two groups. During ischemia, MAP duration at 90% repolarization (MAPD90) decreased significantly, while during reperfusion a significant prolongation of MAPD90 was observed in LAD region similar in both groups. During reperfusion ET-1 and big-endothelin levels increased significantly similar in both groups. ET-1 level increased significantly higher during ischemia in dogs with VF compared to dogs surviving ischemia and reperfusion (survival vs. VF: control: 15.1±1.3 vs. 15.2±1.3 fmol/ml; ischemia 30': 17.6±1.2 vs. 22±1.6 fmol/ml, $p<0.05$). Conclusion: Although endothelin level was increased during reperfusion, LU did not affect the repolarization changes and did not have antiarrhythmic effect during either ischemia or reperfusion, probably due to the multifactorial origin of arrhythmias.

P1180 Cardioprotective effect induced by brief exposure to nitric oxide before myocardial ischaemia-reperfusion in vivo

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Background: Administration of nitric oxide (NO) donors during ischaemia and reperfusion protect from myocardial injury. It is, however, unknown whether administration of an NO donor during a brief period prior to ischaemia protects the myocardium and the endothelium against ischaemia-reperfusion injury in vivo.
Methods: Anaesthetised pigs were subjected to 45 min ligation of the left anterior descending coronary artery (LAD) followed by 4 h of reperfusion. In dose-finding experiments, vehicle or three different doses of the NO donor S-nitroso-N-acetyl-D,L-penicillamin (SNAP, 0.1; 0.5; 2.5 μmol) were infused into the LAD during 3 min starting 13 min before ischemia. Infarct size, endothelium-dependent responses to substance P and myocardial myeloperoxidase activity were evaluated.
Results: Only the 0.5 μmol dose of SNAP reduced infarct size (from 85±3% of the area at risk in the vehicle group to 63±3% in the SNAP treated group ($p<0.01$). There were no significant differences in haemodynamics between the vehicle and SNAP groups during ischaemia-reperfusion. Endothelium-dependent dilatation of coronary microvasculature induced by substance P was larger in the SNAP group than in the vehicle group. Myeloperoxidase activity was lower in the ischaemic/reperfused myocardial area of pigs given SNAP (4.97±0.61 U/g) than in vehicle treated pigs (8.45±0.25 U/g; $p<0.05$).
Conclusions: Intracoronary administration of the NO donor SNAP for a brief period before ischaemia reduces infarct size, attenuates neutrophil accumulation and improves endothelial function. These results suggest that NO exerts a classic preconditioning-like protection against ischaemia-reperfusion injury in vivo in a narrow concentration range.

P1181 Stress activated protein kinases and ischaemic preconditioning in vivo

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There are controversies concerning about the role of the stress activated protein kinases, p38-MAP and p46/p54 JNKs, in preconditioning (PC). The aim of this study was to evaluate their effect on infarct size (IS) in different modes of PC. Anesthetized rabbits were divided in two equal series consisted of 8 groups each. In the 1st series all the animals were subjected to 30 min ischemia (isc) of the heart and 2 hours reperfusion (rep) with one of the following interventions before isc: Control to no intervention, 1PC to one cycle of 5 min isc/10 min rep, 3PC to three cycles 5 min isc/10min rep and the Aortic Clamp group (AoC) to a 5 min mechanical obstruction of the aorta with hypertensive response and 10 min rep which simulated PC. Four more groups, called Gd-Control, Gd-1PC, Gd-3PC and Gd-AoC were respectively subjected to the previous manipulations but they additionally received the stretch blocker gadolinium (Gd); the IS was evaluated. In the 2nd series of experiments, 8 groups of animals were subjected to the same protocol as in the 1st up to the 20th min of isc when the hearts were harvested for p38-MAPK and JNKs assessment. Results: The IS was 42.0±4.4% in Control and 14.2±3.4%, 12.9±3.0%, 15.9±3.3% respectively in 1PC, 3PC and AoC ($P<0.01$ vs Control). Gd did not change IS in Gd-Control (46.2±6.7%), Gd-1PC (16.9±4.2%) and Gd-3PC (15.2±3.7%) but only in Gd-AoC (46.9±4.5%, $p<0.01$ vs AoC); p38-MAPK, p46 and p54 were respectively activated 3.5 to 4.5-fold, 7 to 11-fold and 6 to 7-fold above the control values, independently of the way of PC. The addition of Gd returned the activation of these proteins to baseline values. Conclusion: PC with isc or aortic-clamping are equally effective in reducing the IS and in activation of stress proteins. Although Gd significantly decreases their activation it does not abrogate the beneficial effect of ischemic PC on IS. Thus, p38-MAP and p46/p54 JNKs are involved but with no critical role in the protective mechanism of PC.

P1182 Calcium channel blockade reduces glibenclamide-induced deleterious effects on arrhythmia appearance and diastolic function in conscious sheep

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Introduction: Second generation sulfonylurea compounds have been shown to exert deleterious cardiovascular effects in laboratory and clinical practice. Although the exact mechanism is not fully known, it has been postulated that the KATP channel blockade is the most plausible explanation since KATP channels protect against ischemia-reperfusion damage by reducing Ca^{2+} overload. At present it is not known whether sulfonylureas affect arrhythmia appearance and diastolic mechanical function during ischemia and reperfusion and whether their effects might be due to a Ca^{2+} overload mechanism.
Material and Methods: 23 Hampshire Down sheep underwent a 12 min ischemia followed by 1 h reperfusion after being randomly ascribed to one of the following groups: a) control (C, n=8), b) glibenclamide 0,4mg/Kg 30 min before ischemia (n=8) and c) glibenclamide plus diltiazem (n=7), same as b) with diltiazem (40 micro g/Kg) infused 10 min before ischemia. Arrhythmia appearance and severity were evaluated according to the Lambeth convention and Bernauer's severity index (BSI) while diastolic function was assessed by calculating % radial compliance variations (RC) during ischemia and reperfusion with respect to the basal value considered as 100%.
Results: glibenclamide worsened RC during ischemia (52±4.3 vs C= 76±3.4, $p<0.05$) and reperfusion (75±5.1 vs C= 100.2±2.6, $p<0.05$) and resulted in an increase of BSI (9±0.8 vs C: 4±0.3, $p<0.01$). Interestingly, the addition of diltiazem was capable of eliminating both pro-arrhythmic (BSI: 3,5±0.4, $p<0.01$) and pro-stunning effect of glibenclamide during ischemia (RC: 77±4.3, $p<0.05$) and reperfusion (RC: 98±2.7$p<0.05$).
Conclusions: calcium channel blockade eliminates glibenclamide-induced arrhythmias and diastolic dysfunction. This seems to corroborate that KATP channel blockade determines Ca^{2+} overload injury accounting for the deleterious cardiovascular actions of sulfonylureic compounds.

P1183 Induction of IEX-1, an NFkappaB-dependent gene that controls hypertrophy, by hypoxia and myocardial infarction

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We previously identified the immediate early growth and survival related gene IEX-1 as a biomechanically regulated gene in vitro and in vivo (De Keulenaer et al., Circ Res 2002). In cardiomyocytes, IEX-1 is an NFkappaB target gene and negatively regulates hypertrophy, suggesting that IEX-1 participates in ventricular remodeling. In the present study, we tested the hypothesis that IEX-1 is involved in ischemic cardiomyopathy in vitro and in vivo. Using an in vitro model of neonatal cardiomyocytes exposed to hypoxia (1% O2), Northern analysis demonstrated that IEX-1 expression rapidly increased within 2 hours of hypoxia reaching a maximum at 8 hours, whereas VEGF expression only increased after 24 hours of hypoxia. Induction of IEX-1 was consistent with a 2 fold increase of NFkappB activity by hypoxia (1% O2, 1 hour), as quantified by NFkappB-dependent luciferase activity. To further extend these in vitro observations, male FVB mice underwent coronary ligation, and myocardial IEX-1 expression was analyzed by in situ hybridization and immunohistochemistry. Interestingly, IEX-1 transcripts were detected in the infarct border zone, but not in the infarct region or in intact myocardium. Furthermore, when samples were analyzed by immunohistochemistry, a similar distribution of IEX-1 protein in the infarct border zone was observed, with a specific localization in cardiomyocytes. In conclusion, in the present study we demonstrated induced expression of the NFkappaB-target gene IEX-1 in hypoxic cardiomyocytes in vitro and in the infarct border zone in vivo. We postulate that IEX-1 may participate in early remodeling after myocardial ischemia.

P1184 Improved endothelial and myocardial function by an ETA/B receptor antagonist during ischaemia and reperfusion via a NO-dependent mechanism

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Endothelin (ET) receptor antagonists protect from ischaemia-reperfusion injury. We hypothesized that the the cardioprotective effect of the dual ETA/ETB receptor antagonist bosentan during ischaemia and reperfusion is related to nitric oxide (NO) bioavailability.
Method: Buffer-perfused rat hearts were subjected to 30 min ischaemia and 30 min reperfusion. At the onset of ischaemia the hearts received 3 ml of vehicle, bosentan (10μM), the NO synthase inhibitor L-NNMA (100μM), the combination of bosentan and L-NMMA or the combination of bosentan, L-NMMA and the NO substrate L-arginine (1mM). The NO levels in the coronary effluent were analyzed.
Results: The recovery of myocardial function was poor in the vehicle group. Administration of bosentan resulted in significantly improved myocardial contractile function during reperfusion. The recovery of rate-pressure product (left ventricular x heart rate) was 65±9% in the bosentan group compared to 25±6% in the vehicle group ($P<0.001$). The improved myocardial function induced by bosentan was inhibited by co-administration with L-NMMA (39±8% recovery in rate-pressure product; $P<0.05$ vs. bosentan). Addition of L-arginine restored the cardioprotective effect of bosentan. The recovery of NO release during reperfusion was better preserved in the bosentan group than in the vehicle group (63±10% vs. 39±6%; $P<0.01$). The endothelium-dependent vasodilator adenosine diphosphate increased coronary flow by 18±9% at the end of reperfusion in the bosentan group, whereas it reduced coronary flow by 7±5% in the vehicle group ($P<0.001$).
Conclusion: The dual ETA/ETB receptor antagonist bosentan preserves endothelial and cardiac contractile function during ischaemia and reperfusion via a mechanism dependent on maintained NO production.

P1185 Absence of PK-C loses cardioprotection induced by preconditioning in mice

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Background: Ischemic preconditioning confers cardiac protection during subsequent ischemia-reperfusion, in which protein kinase C (PKC) is believed to play an essential role. Most of our knowledge concerning the role of PKCs in preconditioning comes from studies using a variety of PKC inhibitors, and some controversy exists especially concerning the involvement of PKC isoforms.
Methods: In the present study we investigated the role of PKCdelta (PKCd) in preconditioning using PKCd-knockout mice generated in our laboratories. Both PKCd-/- and PKCd+/+ mice underwent three cycles of 5-minute left descending artery occlusion/5-minute reperfusion followed by a 30-minute occlusion and 2-hour reperfusion.
Results: In wildtype mice serum concentrations of creatine kinase-MB were higher than those in PKCd-deficient mice induced by 30-min ischemia and 2-hour reperfusion. Preconditioning of wildtype mice significantly reduced serum levels of creatine kinase-MB ($p<0.05$). Unexpectedly, about 3-fold enhanced release of cardiac damage markers in PKCd-deficient mice was observed (CK-MB, 1376±286 vs. 5021±355; $p<0.001$). Histological analysis of cardiac tissues revealed that preconditioning treatment resulted in less cardiac damage in PKCd+/+ mice, but traumatic injury in PKCd-/- mice. The damage score was significantly decreased in wildtype mice after preconditioning, while markedly cardiac damage in PKCd-/- mice was found. Furthermore, preconditioning treatment resulted in significantly increased O2- production in hearts of PKCd+/+ mice, and no changes in PKCd-/- animals, indicating the involvement of PKCd-dependent free radical induction.
Conclusions: Our findings demonstrated that PKCd is essential for the cardiac protective effects of preconditioning, implicating the importance of PKCd as a target for therapy.

P1186 Heart rate reduction and negative inotropism exert contrasting cardioprotective effects during exercise-induced ischaemia and stunning in dogs

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The effects of heart rate (HR) reduction induced either by the selective If channel inhibitor ivabradine or the beta-blocker atenolol were assessed on exercise (Ex)-induced myocardial ischemia and stunning in 7 dogs chronically instrumented to measure left ventricular (LV) wall thickening (Wth) and coronary blood flow (CBF). Coronary artery stenosis was set up to suppress the increase in CBF during a 10 min treadmill Ex. When administered before Ex, HR was similarly reduced by ivabradine and atenolol at rest (-18%) and during Ex (-28%) vs saline. During Ex under saline, LVWth dramatically decreased from 29±4% to 2±1% in the ischemic zone. This depression was strongly limited with ivabradine (LVWth=10±3%, $p<0.05$ vs saline) and further reduced by atenolol (LVWth=17±4%, $p<0.05$ vs saline and ivabradine). After completion of Ex, ivabradine significantly reduced the severity of myocardial stunning whereas atenolol failed to improve LVWth vs saline. Interestingly, when administered after the end of Ex, the intensity and severity of myocardial stunning was still strongly reduced by HR reduction with ivabradine and this effect disappeared when HR reduction was abolished by atrial pacing. In contrast, administration of atenolol after the end of Ex was unable to improve myocardial dysfunction and importantly, LVWth was further severely depressed vs saline. In conclusion, this study confirms the beneficial role of HR reduction during myocardial ischemia. Importantly, it also demonstrates the interest of a selective bradycardic agent devoid of negative inotropic activity rather than a beta-blocker in the management of myocardial stunning.

P1187 Histochemical and ultrastructural characterisation of arrhythmogenic cellular substrate in ischaemic pig heart

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Pig heart by its size, coronary anatomy, presence of M cells and intramural Purkinje fibers as well as susceptibility to ischemia/reperfusion-induced lethal arrhythmias is close to human heart, thus useful for the study of arrhythmogenesis. Since survival of endocardial Purkinje fibers after myocardial infarction was shown to be highly arrhythmogenic in dog heart, the aim of this study was to reveal by in situ enzyme histochemistry and examination of ultrastructure the anatomic substrate that could underlie electrical instability of the ischemic pig heart.
Methods: Experiments were performed on anaesthetized landrace pigs (32-40 kg b.w.). The heart was subjected to 90 min of left coronary occlusion followed by 30 min reperfusion. At the end of experiments transmural tissue blocks from the left ventricle containing ischemic, border and nonischemic area were frozen in liquid nitrogen for histochemistry. Small tissue blocks from epi-, mid-, and endo-cardium of all three regions were fixed with 2.5% glutaraldehyde for ultrastructure examination.
Results showed besides ordinary contractile cardiomyocytes and Purkinje fiber also presence of "transitional cells" in midmyocardium that likely correspond to electrophysiologically detected M cells. Importantly, these cells and particularly Purkinje fibers in mid- and subendocardium revealed reversible ischemia-related subcellular alterations different from majority of irreversibly injuried contractile cardiomyocytes. In correlation with these findings, in situ histochemistry revealed abolished glykogen-dependent phosphorylase activity in ischemic area, while still persistent in Purkinje fibers and small islands of cardiomyocytes. Moreover, coronary occlusion followed by reperfusion induced marked heterogeneity in activity of all selected enzymes as well as heterogeneity of subcellular alterations, within a border zone.
Conclusion: The results indicate that preserved viability of specialized conducting cells spanning severely ischemic ventricular wall can underlie anatomic substrate for electrical disturbances facilitating re-entry that consequently increase of susceptibility of the pig heart to ischemia- and reperfusion- induced lethal arrhythmias.

P1188 Complete abolishment of increased myocardial ischaemia-reperfusion injury conferred by hypercholesterolemia through inhibition of caspase-1 cascade

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Objective: Hypercholesterolemia is associated with greater myocardial ischemia-reperfusion injury, in which apoptosis and inflammation-mediated necrosis both play a key role. Caspase-1 is involved in the activation of both apoptosis and inflammation, through the intermediate of interleukin-1b(IL-1b). In this study, we examined whether pharmacological inhibition of the caspase-1 cascade, using Ac-YVAD.cmk, after myocardial ischemia have greater protective effects on myocardial ischemia-reperfusion injury in diet-induced hypercholesterolemic rabbits.
Methods and results: Sixty male New Zealand White Rabbits, fed with standard chow or chow supplemented with 1% cholesterol for 8 weeks, were subjected to 30 minutes of left circumflex artery occlusion followed by 4 hours of reperfusion. An intravenous bolus of Ac-YVAD.cmk (1.6 mg/kg) or vehicle was given 20 minutes after coronary occlusion in each group. The infarct size (% of risk region) was significantly greater in cholesterol-fed rabbits than in normally fed ones (41±6% vs. 26±3%, P=0.003). Postischemic administration of Ac-YVAD.cmk markedly decreased infarct size from 26±3% to 12±2% in normally fed rabbits (P=0.005) and from 41±6% to 14±2% in cholesterol-fed rabbits ($P<0.001$). In the ischemic non-necrotic area, the percentage of TUNEL-positive cardiomyocytes was significantly greater in vehicle-treated cholesterol-fed rabbits compared with normally fed ones (39.0±2.3% vs. 15.5±0.8%, $P<0.001$), whereas treatment with Ac-YVAD.cmk markedly reduced the percentage of TUNEL-positive cardiomyocytes from 15.5±0.8% to 2.2±0.1% in normally fed rabbits ($P<0.001$) and from 39.0±2.3% to 2.2±0.1% in cholesterol-fed rabbits ($P<0.001$). Although myocardial IL-1b levels and activity of both caspase-1 and caspase-3 in the ischemic area were significantly higher in vehicle-treated cholesterol-fed rabbits compared to normally fed ones, Ac-YVAD.cmk treatment resulted in a reduction not only of IL-1b and caspase-1, but also of caspase-3 in both normally fed and cholesterol-fed rabbits. Furthermore, no differences in IL-1b levels and activity of caspase-1 and caspase-3 were observed between Ac-YVAD.cmk-treated normally fed and cholesterol-fed rabbits.
Conclusion: This study demonstrates that injection of a selective caspase-1 inhibitor after myocardial ischemia completely abolished the detrimental effect conferred by hypercholesterolemia on myocardial ischemia-reperfusion injury by attenuating both necrotic as well as apoptotic cell death pathways through inhibition of IL-1b production and activation of caspase-1 and caspase-3.

P1189 The postischaemic functional recovery of the myocardium is reduced by endogenous endothelin-1

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Elevated plasma levels of the potent vasoconstrictor Endothelin-1 (ET-1) were observed in patients with coronary heart disease. The release of this peptide from the damaged endothelium may play a role in the initiation and maintenance of myocardial ischemia. This study examines the ETA-receptor mediated role of endogenous endothelin on postischemic myocardial function after prolonged hypoperfusion.

Methods: In an isolated rat heart model after 3h hypoperfusion (15% of preischemic coronary flow) followed by 2h reperfusion postischemic left ventricular functional recovery was determined (isovolumic steady state hemodynamics: LVP, dP/dtmax; maximal inotropic response: max LVP, max dP/dtmax). The effect of ET conversion inhibition by phosphoramidon (PHOSPH, 2 μmol/l) and of ETA-blockade by BQ 610 (0.8 μmol/l) during hypoperfusion was compared to saline controls (NaCl).

Results: 2h of reperfusion after hypoperfusion causes a partial functional recovery. This recovery is significant better after ECE-inhibition or after ETA-blockade.

	coronary flow	LVP	dP/dtmax	max LVP	max dP/dtmax
PHOSPH	57.7±4.1	58.2±2.5#	61.9±3.7#	73.3±10.3	74.1±17.0
BQ 610	54.1±5.0	56.0±2.5#	54.8±2.8¶	85.1±5.6*	84.5±6.3
NaCl	49.3±2.4	36.5±2.1	41.1±1.1	58.6±5.6	59.1±13.5

Mean ± SEM in % of preischemic values after 2h of reperfusion; *=p<0.05, ¶=p<0.01, #=p<0.001 vs. NaCl-group.

Conclusions: 2h after termination of hypoperfusion reperfused myocardium profits from ECE-inhibition or ETA-blockade during the prolonged period of hypoperfusion. This indicates that the postischemic functional recovery is reduced by endogenous ET-1 via ETA-receptors.

P1190 Low blood pressure during reperfusion reduces coronary flow and increases myocardial infarct size

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Objective: The purpose of this study was to examine the effect of low blood pressure during reperfusion on the extent of myocardial infarction and on coronary blood flow (CBF) in an occlusion/reperfusion experimental model.

Methods: Twenty seven open chest pigs (22-35Kgr) underwent occlusion (O) of the middle left anterior descending coronary artery (LAD) for 1 hour followed by reperfusion for 2 hours. During reperfusion the animals were assigned to two groups; Continuous nitroglycerin infusion and fluid infusion at the appropriate rates were used to maintain mean arterial pressure (MBP) > 80mmHg in Group I (n=13) versus 60-75mmHg in Group II(n=14). The LAD coronary arterial flow was measured by transit time flowmetry and the hemodynamics and the distal to O coronary arterial pressures, were recorded before the O of the LAD and throughout the experiment. Blood pressure, heart rate, right and left atrial pressures were continuously monitored, and at the end of 3 hours, the infracted myocardium of the left ventricle was determined and expressed as the percentage of the myocardium at risk.

Results: There were no significant hemodynamic differences between the two groups before or during the LAD occlusion. During reperfusion the MBP was 89.9±3.3mmHg in Group I vs 68.7±2.5mmHg in Group II (p=0.000). In Group I the infracted myocardium was 50.3±4.3% of the myocardium at risk and in Group II 69.4±7.2% (p=0.000). During reperfusion the CBF in Group I was significantly higher than than in Group II. The CBF normalized to control level was follows: at first min 3.51±1.11 vs 2.24±1.29, p=0.097, at 5 min 2.94±0.34 vs 1.55±0.74, p=0.004, at 15 min 2.57±0.60 vs 1.24±0.74, p=0.011, at 60 min 2.01±0.69 vs 1.18±0.40, p=0.002, and at 120 min 1.41±0.88 vs 0.86±0.47, p=0.114 in Group I vs II respectively.

Conclusion: Low blood pressure during reperfusion increases the extent of myocardial infarction. This effect is most likely due to greater impairment of the coronary circulation accompanying the low blood pressure during reperfusion.

P1191 The protective effect of isosorbide dinitrate on cardiac mitochondria during ischaemia is not mediated by nitric oxide

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Nitrates are one of the drugs more frequently used in the treatment of myocardial ischemia. Their anti-ischemic effect seems to be mediated by nitric oxide.

The aim of our study was to determine if the Isosorbide Dinitrate's (IDN) protective effects on the cardiac mitochondrial metabolism are also mediated by the release of nitric oxide.

We used an ex-vivo global myocardial ischemia model, with the use of a Lagendorff perfusion system. Forty Wistar rat's hearts were divided in 4 experimental groups - A (180 minutes of perfusion, with a Krebs modified solution), B (60 minutes of perfusion with the same solution, followed by 120 minutes of ischemia), C (as in B, but in the presence of IDN 1 mM) and D (as in B, but in the presence of IDN 1 mM and an nitric oxide synthase inhibitor: L-NAME 100 μM). Mitochondria were isolated and used to evaluate the activity of complexes I, II-III and IV of the mitochondrial respiratory chain (MRC), using their metabolic substrates (Glutamate/Malate, Succinate and Ascorbate/TMPD). The parameters evaluated were: Respiratory Control Ratio (RCR), O2 consumption during state 3 of mitochondrial respiration (S3), Maximal Mitochondrial Membrane's Electrical Potential (Delta Psi), Phosphorylative Lag Phase (PLP), Energetic Charges (EC) and Enzymatic Activities (EA) of each of the MRC complexes.

In the conditions studied, IDN decreased significantly S3 and was able to reduce the PLP to all the substrates considered; regarding Delta Psi, the result was globally positive, but only statistically significant when Glutamate/Malate was used. Values of EC, RCR and EA of Complexes I and IV were not significantly altered, while the EA of Complexes II-III was statistically superior to that of the ischemic group. In the group treated with L-NAME, the results were similar to those of the IDN group.

Results:

Groups/Parameters	IDN (Group B)	IDN + L-NAME (Group C)	p value (B vs. C)
Delta Psi (Glutamate/Malate)	98±1.5%	93.6±1.6%	p=n. s.
PLP (Succinate)	120.6±19.8%	111.1±18.5%	p=n. s.
EC (Glutamate/Malate)	81.9±5.2%	74.6±8.3%	p=n. s.
EA (Complexes II-III)	343.5±35.3%	369.9±26.4%	p=n. s.

Note: Values are expressed as % of control (Group A).

In conclusion, our study demonstrate that the cytoprotective effects of IDN on cardiac mitochondrial metabolism are not mediated by the release of nitric oxide.

P1192 Calcitonin gene related peptide mediates cardioprotection after remote preconditioning

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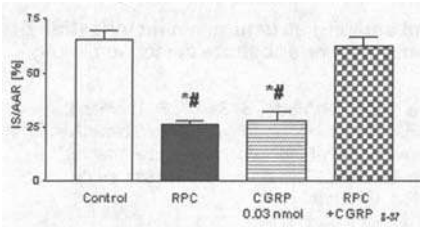
Objective: Brief ischemia-reperfusion periods of remote organs protect the heart from a pro-longed ischemic injury. Kinins and neuronal reflexes including sensory nerves contribute to the transduction of such remote preconditioning (RPC) to the heart. Because calcitonin gene related peptide (CGRP) is a well known mediator of sensory neurons we tried to delineate whether CGRP a) protects the heart from ischemic injury, b) is involved in cardioprotection after RPC, and c) leads to an activation of myocardial protein kinase C (PKC) e, a possible candidate for intracellular signal transduction of RPC.

Methods: Anesthetized rats pretreated with CGRP (0.03 nmol/kg) were subjected to 30 min of coronary artery occlusion followed by 150 min of reperfusion. Myocardial infarct size (IS) was measured by TTC staining and expressed as percentage of the area at risk (AAR). In separate experiments, RPC was achieved by brief mesenteric artery occlusion followed by reperfusion, in the presence or absence of CGRP8-37 (3 nmol/kg), a selective CGRP receptor antagonist. Rats either under-went myocardial infarction or PKCe was measured in myocardial membranes and cytosol by quantitative immunoblotting.

Results: IS/AAR% was significantly reduced in rats that received CGRP (28±4%) as compared with those receiving saline (65±5%). RPC significantly reduced infarct size (26±2%) and shifted the ratio between cytosolic and particulate PKCe, an indicator for PKC-activation, from 0.54±0.05 in controls to 0.21±0.03 (p<0.05). Infarct size reduction was abolished and PKC activation was significantly attenuated by CGRP8-37.



CGRP reduces infarct size.

Conclusions: CGRP protects the heart from ischemic injury and is involved in RPC, presumably by activating myocardial PKCe.

P1193 Remodeled myocardium: a new concept in heart failure

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Introduction: Coronary artery disease is the leading cause of heart failure. Chronic ischemic syndromes (hibernating and stunned myocardium) have been identified and contribute to myocardial dysfunction. Most patients however develop heart failure insidiously after an acute MI without any further ischemic insults, suggesting that the infarct initiates a myopathic process in normally perfused myocardium.

Methods: In 6 sheep, 8 piezoelectric transducers were sutured within the myocardium of the long axis of the anterior wall of the left ventricle (LV). This allowed measurement of contraction in discrete segments of LV myocardium. Two weeks following instrumentation previously placed coronary snares were tightened, producing an antero-apical MI of 23% of the LV mass. Sonometric and hemodynamic data are collected pre-infarct and at 30 minutes, 2, 5 and 8 weeks postinfarction. Serial microsphere injections are performed at the 2, 5 and 8 week studies. Myocardial specimens are obtained using the sonometric transducers as markers thus allowing direct correlation of perfusion and functional data.

Results: Contractility in the infarct stopped immediately postinfarction and did not recover. The myocardium outside the infarct remained normally perfused throughout the study. Contractility of myocardium adjacent to the infarct decreased after the infarction. This hypocontractile region expanded and became more dysfunctional during the study period, despite unchanged perfusion. The table below presents percent change in contraction as compared to baseline in the remote, remodeled and infarcted myocardium at 30 minutes, 2 weeks, 5 weeks, and 8 weeks postinfarction.

Timepoint Post-infarction	Remote	Remodeled	Infarct
30 minutes	29.9%	46.2%	-182.6%
2 weeks	66.1%	25.2%	-158.6%
5 weeks	46.6%	-31.6%	-188.0%
8 weeks	14.9%	-96.8%	-163.5%

Conclusions: Postinfarction ventricular remodeling initiates a myopathic process in the noninfarcted myocardium that is initially localized to the region adjacent to the infarct but progressively expands to involve increasing amounts of normally perfused myocardium.

P1194 Interleukin-2 inhibition improves left ventricular function after induction of experimental myocardial infarction

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Cardiac ischemia is accompanied with an increase in pro-inflammatory cytokines including interleukine-2 (IL-2).However, the role of IL-2 after induction of myocardial infarction (MI) is not known. We investigated the effect of an interleukin-2-fusion-protein (IL-2-IgG2b fusion protein) on ventricular function after induction of MI in a rat model.

Male Sprague-Dawley rats were submitted to a permanent occlusion of the left descending coronary artery or to a time-matched sham operation. Six hours before induction of MI rats were treated with a specific Il-2-fusion-protein or with vehicle and continued in a daily dose of 330µg for each animal (n=8 per group). 24h, 6 days or 3 w after operation, a Millar-tip-catheter was placed in the LV and LV pressure (LVP) and contractility (LVdp/dt max) were determined in anaesthetised and ventilated in open-chest animals. Finally, hearts were excised immediately for immunhistochemical examinations regarding IL-1β and collagen expression.

We found a decrease in LVP and contractility 24h (LVP: 56.8±2.4 vs. 80.9±4.2 mmHg; dp/dt max: 2620±158 vs. 3617±245 mmHg/sec; P=0.05) and 6d (LVP: 52.3±3.8 vs. 76.9±2.4;dp/dt max: 4423±261 vs. 2527±153 mmHg/sec; P = 0.05) after induction of MI compared to sham operated animals The impaired cardiac function was improved in animals treated with a IL-2-fusion-protein 24h post infarction (LVP: 72.8±3.6 mmHg; dp/dt max 3187±376 mmHg/sec). This improvement was also seen 6 d and 3 w after induction of MI. Improvement of LV function correlated with a reduction in cardiac IL-1β and collagen expression. No differences regarding the size of the infarcted area in the MI groups could be detected.

We present the first data for a selective blockade of Il-2 providing a significantly improvement of left ventricular function in experimental MI.

P1195 Macrophage migration inhibitory factor as a redox-sensitive cytokine in cardiomyocytes

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Macrophage migration inhibitory factor (MIF) plays a pivotal role in the control of inflammatory responses. Accumulating evidences indicate that inflammatory responses is associated with ischemic heart diseases. However, little is known about the MIF in the myocardium. We investigated the MIF production in patients with acute myocardial infarction (AMI), and the MIF's expression and role in the myocardium in vitro. MIF plasma levels were markedly elevated on day 1 and then decreased on days 7-21, but the levels on days 7 and 14 were still significantly higher than those in normal subjects. In contrast, although MIF levels in the supernatant of cultured peripheral blood mononuclear cells (PBMCs) from patients on day 1 after the occurrence of AMI showed no significant increase compared with those from normal subjects, the levels increased significantly on days 7-14. These findings suggest that the MIF production in patients with AMI differ between the acute and subacute stages of AMI by necrotic cardiomyocytes and activated mononuclear cells, respectively. To further investigate the MIF's expression and role in cardiomyocytes, we used cultured neonatal rat cardiac myocytes and showed that MIF production and mRNA expression were stimulated in response to hypoxia and hydrogen peroxide (H2O2), but not to angiotensinII, endothelin-1, interleukin-1, or tumor necrosis factor. H2O2-induced MIF production increased in a time- and dose-dependent manner and was completely abolished by the presence of catalase. The H2O2-induced MIF production was completely inhibited by the PKC inhibitor GF109203X, partially inhibited by the tyrosine kinase inhibitor herbimycin A, and uninhibited by calcium chelation or phorbol ester-sensitive PKC down-regulation. This suggests that H2O2-induced MIF production is mediated by an atypical PKC isoform. Furthermore, DNA microarray analysis revealed that 52 genes were preferentially expressed in response to MIF. Of these, the MIF-induced expression of glutathione S-transferase (GST), lipopolysaccharide-induced CXC chemokine (LIX), and insulin-like growth factor-binding protein (IGFBP-3) mRNAs was confirmed by RT-PCR analysis. These findings suggest that MIF is expressed by the cardiomyocytes in response to redox stress, and provide new insight into the pathological role of MIF in AMI.

P1196 T4 pretreatment and ischaemic preconditioning have additive cardioprotective effect possibly mediated by p38 MAPK attenuation during ischaemia

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Introduction: Long-term thyroxine administration has been shown to protect the heart agaist ischaemic injury. This cardioprotection is associated with acceleration of ischaemic contracture (IC) and decreased activation of p38 MAPK during ischaemia and reperfusion. Ischaemic preconditioning (PC) is another cardioprotective mechanism that lowers preischaemic glycogen levels and thus accelerates IC. p38 MAPK attenuation has also been implicated in the protection conferred by PC. We investigated whether these two cardioprotective mechanisms exert an additive effect and whether this effect is associated with further decrease in activation of p38 MAPK in response to ischaemia-reperfusion (I/R) in the isolated rat heart.

Methods: Male Wistar rats were treated with L-Thyroxine (25ig/100g) subcutaneously once daily for 14 days (THYR) while normal rats treated with normal saline served as controls (NORM). The isolated hearts were perfused in the Langendorff mode and were subjected to the following protocols: 1) 20 min of stabilisation followed by 20 min of zero-flow global ischaemia (I), NORM(I), n=4 and THYR(I), n=4 2) 20 min of stabilisation followed by 20 min of I and 45 min of R, NORM(I/R), n=6 and THYR(I/R), n=6 3) 20 min of stabilisation followed by two cycles of PC (3min I, 5min R, 5min I, 5min R) and then 20 min of I, THYR-PC(I), n=4 and 4) 20 min of stabilisation followed by PC, 20 min of I and 45 min of R, THYR-PC(I/R), n=6. The postischaemic recovery of function was assessed by the recovery of left ventricular developed pressure (LVDP) expressed as % of the initial value (LVDP%). The acceleration of ischaemic contracture was assessed by the time to peak IC in min (Tmax). The levels of phosphorylated and total p38 MAPK were measured by Western blot analysis.

Results: LVDP% was 37.2(4.5) in NORM(I/R), 54.9(5.5) in THYR(I/R) and 77.9(4.5) in THYR-PC(I/R), $p<0.05$ between all groups. Tmax was 18.6(0.7) min in NORM(I/R), 12.4(0.4) min in THYR(I/R) and 6.1(0.6) min in THYR-PC(I/R), $p<0.05$ between all groups. Phosphorylated p38 MAPK was 1.9 fold higher in NORM(I) than in THYR(I), $p<0.05$ and 3.3 fold higher in THYR(I) than in THYR-PC(I), $p<0.05$. At the end of the reperfusion period phosphorylated p38 MAPK was 1.7 fold higher in NORM(I/R) than in THYR(I/R), $p<0.05$ while there was no significant difference between THYR-IR and THYR-PC-IR.

Conclusion: Thyroxine pretreatment and ischaemic preconditioning have additive cardioprotective effect. This protection might be due to profound attenuation of p38 MAPK activation during sustained ischaemia.

P1197 Myocardial protection via delta-opioid receptor activation in the isolated working rabbit heart

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Objective: Delta-opioid receptors are known to mediate natural hibernation and are involved in ischemic preconditioning. In an experimental model of ischemia and reperfusion the protective capacity of the synthetic delta-opioid receptor agonist D-Ala(2)-D-Leu(5) enkephalin (DADLE) was assessed, and it was compared with the capacity of mannitol, a potent non-specific free-radical scavenger. In addition, the protection after administration of both agents was assessed.
Methods: 28 isolated, blood-perfused working rabbit hearts were subjected to 20 min of normothermic ischemia followed by 60 min of normothermic reperfusion. Rabbit hearts were pre-treated with DADLE (D, 440 nM, n=8), mannitol (M, 8.5 mM, n=7), or a combination (D+M, n=8). The postischemic functional recovery of the hearts and troponin T (TnT) concentration were determined.
Results: Pre-treatment with DADLE alone and in combination with mannitol reduced significantly ischemic contracture by 21% and 58%, respectively. Postischemic recovery of aortic flow, when compared with non-treated hearts, was significantly improved (D 60.7% ± 11.0% and M 67.8% ± 14.3% and D+M 69.0% ± 14.2% of preischemic baseline). Myocardial oxygen consumption was also improved after pre-treatment compared with untreated hearts (D 76.7% ± 8.6% and M 80.8% ± 6.3% and D+M 79.0% ± 7.3% of preischemic baseline; $p < 0.05$), as well as an external efficiency index (stroke work/MVO2; D 76.7% ± 9.5% and M 84.8% ± 6.3% and D+M 71.0% ± 8.2% of preischemic baseline; $p < 0.05$). With DADLE pre-treatment, early postischemic TnT release was lower than M and control (0.28 ± 0.11 vs. 0.38 ± 0.09 vs. 0.48 ± 0.12 ng/ml at 60 min reperfusion; $p < 0.05$).
Conclusions: We provide experimental evidence that functional protection is effectively mediated via pharmacologic activation of delta-opioid receptors or scavenging oxygen-derived radicals (mannitol) in isolated, blood-perfused, working rabbit hearts. Since the combination of both protective agents did not provide an additional effect, we suggest that both protective measures act via a common pathway, e.g. attenuation of oxidant stress. Pre-treatment with DADLE reduces more effectively ischemic cellular injury, i.e. TnT degradation, and further adds to postischemic functional recovery.

P1198 Reduction of myocardial infact size by fluvastatin

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Endothelial dysfunction with a decreased availability of NO is causatively involved in the development of reperfusion injury not only by the reduction of endothelium-dependent vasodilation but also by an increased expression of cellular adhesion molecules resulting in enhanced extravasation of activated neutrophils. Statins have been shown to improve endothelial cell function by increasing the availability of NO. We, therefore, hypothesized that statin therapy decreases myocardial infarct (MI) size and neutrophil extravasation.
Methods: In an in situ perfused rat heart model, MI was induced by ligation of the left coronary artery (LCA) for 50min, followed by 60min reperfusion. Myocardial blood flow (MBF; hydrogen clearance) and regional myocardial function (MF; pulsed doppler) were measured continuously during the experiments. MI size was determined by TTC staining and expressed as infarcted area/area at risk. Fluvastatin (fluva, 100μg/kg) was given as continuous intravenous infusion starting 20min before the ligation. Neutrophil extravasation was measured by determination of myeloperoxidase activity (MPO). The effect of fluvastatin on NO production was investigated in HUVEC.
Results: Fluva significantly attenuated the decrease of MF and reduced infarct size without influencing the reduction of MBF (control: MF 9.1%, MIsize 70.5%, MBF 1.8ml/min/g; fluva: MF 11.8%, MIsize 53.6%, MBF 1.9ml/min/g. In addition, MPO activity was significantly reduced in the fluva-treated group. In HUVEC, fluva increased cGMP production by 2fold.
Conclusion: These data indicate that exogenous substitution of fluvastatin reduces the size of myocardial infarction by attenuating neutrophil extravasation and possibly by increasing the availability of NO. We, therefore, conclude that statins may be helpful in the prevention of reperfusion injury.

P1199 Cross-talk between nitric oxide and cyclooxygenase metabolic pathways in HUVEC

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Introduction: It is well known that endothelium is involved in the control of vascular integrity and function through the release of both vasodilators, such as nitric oxide (NO), prostacyclin (PGI2) and prostaglandin E2 (PGE2) and vasoconstrictors. The possibility that vessel homeostasis may be maintained through a compensatory mechanism between different metabolic pathways has been proposed. However, the existence of a cross talk between endothelial PGs and NO release has not been completely clarified. Our aim was to evaluate the interaction between NO and prostaglandins (PGs) release in HUVEC, human umbelical vein endothelial cells. Methods: Medium samples were assayed for nitrite/nitrate (NOx) assay (Griess Reaction, Cayman), endothelial NOSynthase quantification (EIA assay, R&D System) and L-citrulline (colorimetric assay based on its reaction with diacetyl monoxime), as markers for NO release. In addition prostaglandin E2 (PGE2) and 6-keto prostaglandinF1alfa (PGF1a, metabolite of PGI2) quantification (EIA assays, Cayman) were evaluated as indicator of COX activity. Six experiments were performed for each 24 hour treatment. Results: L-arginine 100 and 250 μM increased both NOx (mean±SE: from 22.8±1.6 to 28.95±2.7, 38±4cells μM/100000 cells, $p<0.01$) and 6-ketoPGF1a medium levels (from 648.8±59.5 to 1519.2±233.6 and 2291.4±293.8 pg/100000 cells, $p<0.01$). Exposure to sodium nitroprusside 25 μM induced a significant increment in 6-ketoPGF1a levels (852.5±169.3 pg/100000 cells, $p<0.05$). 6-ketoPGF1a and PGE2 medium levels were not affected by NG-monomethyl-L-arginine (L-NMMA) treatment (250, 500, 750, 1000 μM; 336.2±90.1, 583.9±59, 452.4±86.8 and 692.3±106.1 pg/100000 cells, and from 273.2±30.6 to 250.4±29, 238.5±20.1 and 244.3±48.5, 227.4±37.6 pg/100000 cells, respectively). INDO 30 and 100 μM significantly enhanced NOx (37±6.44 and 42.3±6.29 μM/100000 cells, $p<0.05$ and $p<0.01$) and citrulline levels (from 253.4±27.3 to 438±81.4, $p<0.05$ and 478.8±75.5 μM/100000 cells, $p<0.01$, respectively). In addition, eNOS production was significantly enhanced following INDO 100 μM (from 94.6±18.8 to 177.5±32.1 μM/100000 cells, $p<0.05$). Conclusion: Enhanced NO bioavailability significantly increased PGs levels, indicating that the mechanism of action of NO may be partially mediates by vasodilatatory PGs. Inhibition of PGs production with indomethacin, was compensated by the enhanced release of NO. By contrast, inhibition of NOS with L-NMMA did not affect PGs release, that fail to compensate reduced NO levels.

P1200 Atrial natriuretic peptide and NO show cyclic guanosine-monophosphate increasing and vasodilating effects in human coronary bypass grafts

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Objectives: Natriuretic peptides show vasodilatory and antiproliferative effects and therefore, may be protective when applied to human coronary bypass grafts. In this study we wanted to demonstrate that bypass grafts can be stimulated by natriuretic peptides, and that there is a direct link between cyclic-guanosine-monophosphate(cGMP)-concentration and functional relaxation.
Methods: We used remnants of the internal mammary artery (IMA) and the saphenous vein (SV) of 27 patients (median: 71 years) undergoing coronary bypass grafting. 49 rings of the IMA and 29 rings of the SV were tested using the organ bath set-up (Hugo-Sachs-Electronics, Freiburg, Germany). Rings were precontracted with 30 nM U46619 (a thromboxane agonist), and relaxation in response to 300 nM atrial natriuretic peptide (ANP), 300 nM C-type natriuretic peptide (CNP), and 0.1 mM 3-morpholino-sydnonimine (sin-1, a NO liberating substance) was measured by isometric force and calculated in % changes in tension. Rings and supernatant were collected at the end of the experiment to determine intra- and extracellular cGMP concentration by a radioimmunoassay (Amersham, Vienna, Austria).
Results: Controls of the IMA showed sponaneous relaxation of 9.3% at the end of the experiment, whereas the SV remained fully contracted. However, intra- and extracellular cGMP-concentrations were similar. In the IMA, ANP and sin-1 caused significant and comparable relaxation (64% and 61%, respectively; $p<0.001$ each) compared with control rings. Furthermore, there was a significantly increased intracellular production of cGMP in these rings ($p=0.001$ each) compared with control rings. Additionally, extracellular cGMP concentration was significantly increased after ANP stimulation ($p=0.002$) of the IMA. CNP did not cause any significant relaxation or cGMP production in the IMA. In the SV, sin-1 caused significant relaxation (36%; $p<0.001$) and significantly increased intra- ($p=0.005$) and extracellular ($p=0.011$) cGMP concentration compared with controls. ANP and CNP had no significant effects on the SV. Moreover, the IMA produced significantly higher intracellular concentrations of cGMP after ANP and sin-1 stimulation compared with the SV ($p<0.01$ each).
Conclusion: ANP and NO seem to have strong vasodilating and cGMP-stimulating effects on the internal mammary artery, whereas only NO shows these effects in the saphenous vein. CNP appears to be less effective on both vessels.

THROMBOSIS – ENDOTHELIAL FUNCTION

P1201 Natriuretic factors suppress plasminogen activator inhibitor type-1 expression in human preadipocytes

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Background: Human adipose tissue and particularly its preadipocyte cell fraction produce a substantial amount of plasminogen activator inhibitor type-1 (PAI-1), known to contribute to the development of cardiovascular disease. Little is known about natural factors regulating PAI-1 expression in adipose tissue. The present study examines the effect of the atrial natriuretic factor (ANF) and the C-type natriuretic peptide (CNP) on PAI-1 expression in primary cultures of human preadipocytes.
Methods: Human preadipocytes were prepared from subcutaneous abdominal adipose tissue by collagenase digestion. The cells in primary culture were exposed to selected concentrations of ANF 1-28 and CNP 22 (10 nM, 100 nM, 1000 nM) in the presence and absence of transforming growth factor-beta (TGF-beta), a cytokine known to stimulate PAI-1 synthesis in adipose tissue.
Results: Incubation with 10 nM, 100 nM, and 1000 nM ANF reduced basal PAI-1 expression in the conditioned media by 5%, 18%, and 7%. Similarly, CNP downregulated PAI-1 protein concentration by 28%, 23%, and 18% (n=6, $p<0.05$ each). Stimulation with TGF-beta resulted in a 10-fold increase of basal PAI-1 production. Again, 10 nM, 100 nM, and 1000 nM of ANF suppressed stimulated PAI-1 levels by 20%, 22%, and 5%. The same concentrations of CNP reduced PAI-1 synthesis by 46%, 36%, and 22% (n=6, $p<0.05$ each). Expression of the PAI-1 gene as assessed by rt-PCR suggest a transcriptional regulation of PAI-1 expression by ANF and CNP.
Conclusion: ANF and CNP reduce both basal and TGF-beta stimulated PAI-1 expression in human preadipocytes. These observations suggest that both peptides are important natural regulators of PAI-1 synthesis in adipose tissue, and, thereby, are likely to be involved in vascular disease.

P1202 Platelet-leukocyte aggregation under shear stress: different involvement of selectins and integrins

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Background: Platelets and leukocytes can form heterotypic aggregates in vivo, and mutually influence their functions. However, it has not been defined how shear force in the blood stream influences platelet-leukcoyte aggregation (PLA).
Methods: Hirudinized whole blood was stimulated with vehicle or agonists (10 μM ADP or 0.1 μM fMLP) under different levels of shear stress (200, 500, 1000 and 1800 S(-1)), using a cone-and-plate(let) analyzer. PLA and platelet-platelet aggregate (PPA) formation, as well as platelet P-selectin and leukocyte CD11b expression were monitored by whole blood flow cytometry.
Results: Shear stress per se increased platelet P-selectin expression, leukocyte CD11b expression, and PLA formation. More obvious effects on PLA formation were seen with lower shear stress. For example, PLAs were increased from 5.3±0.3% to 12.3±1.5% at 500 S(-1), but only to 8.2±0.7% at 1800 S(-1). Increased heterotypic aggregation was mainly seen among monocytes and neutrophils (from 12.4±2.2 to 38.8±8.3% and from 5.7±1.7 to 14.4±3.5% by 500 S(-1) shear stress, respectively), but not in lymphocytes. ADP markedly increased platelet P-selectin expression (1.8±0.3% to 32.0±3.6%) and thus PLA formation (from 5.3±0.2 to 15.5±3.9%). ADP-induced PLA was, however, reduced by >=500 S(-1) shear stress (9.6±0.6% at 500 S(-1)). fMLP markedly increased leukocyte CD11b expression (1.1±0.2 to 3.4±0.5), but did not increase PLA formation (5.3±0.3 without and 5.6±0.4% with fMLP). In fMLP-stimulated samples, PLA formation was enhanced by shear stress (18.2±4.2% at 500 S(-1)). P-selectin blockade by MAb 9E1 abolished PLA formation induced by shear stress, ADP, or fMLP. In contrast, GPIIb/IIIa blockade by c7E3 enhanced shear-, ADP-, and fMLP-induced PLA formation, presumably by blocking PPA formation and thus increasing the availability of single activated platelets for PLA formation.
Conclusions: Shear stress enhances PLA formation. P-selectin-mediated bridging is necessary to initiate PLA formation, but only supports a loose conjugation, which can be dispersed by high shear stress. GPIIb/IIIa-fibrinogen-CD11b bridging increases the stability of heterotypic conjugation.

P1203 Determinants of soluble P-selectin as a marker of platelet activation in 1316 patients with atrial fibrillation

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Introduction: Abnormal indices of platelet activation have been described in atrial fibrillation (AF), in keeping with a prothrombotic state. However, platelet activation in AF may reflect the presence of underlying atherosclerotic disease rather than increased thromboembolic risk.
Methods: We measured plasma soluble P-selectin (sP-Sel) levels by ELISA in 1315 participants enrolled in the Stroke Prevention in AF (SPAF) III trial, and related sP-sel to conventional risk factors for atherosclerosis and stroke in AF.
Results: Results from univariate analysis are shown in Table 1.

Clinical Factor	Clinical Factor Present	Clinical Factor Absent	p
Age >75 years	34 (13)	34 (13)	0.4
Male	35 (14)	31 (12)	<0.001
Hypertension	34 (14)	34 (12)	0.7
Prior Cerebral Ischaemia	32 (11)	34 (14)	<0.01
Peripheral Vascular Disease	39 (13)	34 (13)	<0.001
Diabetes	36 (15)	34 (13)	0.01
Heart Failure	34 (12)	34 (13)	0.6
Prior Myocardial Infarction	35 (11)	34 (14)	0.1
Serum Cholesterol >median (201mg/dl)	34 (13)	34 (14)	1.0
Current Smoking	38 (14)	34 (13)	<0.01
Moderate-Severe Left Ventricular Dysfunction	33 (12)	34 (11)	0.5

Univariate Associations Between Atherosclerotic and Thromboembolic Risk Factors and Plasma sP-sel Levels (values in pg/ml expressed as mean(sd))

Factors independently associated (adjusted r2 = 4%) with plasma sP-sel level following multivariate analysis were male sex (increased, $p<0.001$), current smoking (increased, p=0.01), peripheral vascular disease (increased, $p<0.001$), diabetes (increased, p=0.01) and prior cerebral ischemia (decreased, p=0.002). There was no difference in sP-sel between those at "high', "moderate" and "low" risk of stroke (SPAF III risk criteria, p=0.3) nor between different antithrombotic therapies (p=0.09).
Conclusion: Among patients with AF, plasma levels of sP-sel were higher in association with four major atherosclerotic risk factors, whereas lower or unaffected by many thromboembolic stroke risk factors. Platelet activation in AF is likely to reflect generalised atherosclerotic disease and may not play a major role in thromboembolism.

P1204 Evaluation of thrombomodulin and platelet activation products in patients undergoing PTCA. Effects of per os L-Arginine

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Introduction: Endothelial denudation during PTCA causes the aggregation and activation of platelets, resulting in the release of intracellular substances, which induce proliferation and migration of smooth muscle cells in the neointima of the vessel wall. This process may lead to acute or subacute thrombosis and later restenosis. Experimental data have shown that Nitric Oxide (NO) inhibits platelet aggregation and activation. The aim of our study was to evaluate the possible beneficial effects of per os L-Arginine, a precursor of NO, on plasma levels of forth Platelet Factor (PF4), b-Thromboglobulin (BTG) and Thrombomodulin (TM).

Methods: We examined 63 male pts (aged 56.5±7.6 years) undergoing elective PTCA, not treated with IIb-IIIa inhibitors. L-Arginine was given in a dose of 21 gr per day, starting 3 days before, up to 1 month after PTCA, to 37 randomly selected pts (group-1). The rest 26 pts received placebo (group-2). All pts were put on conventional treatment for PTCA. Blood samples were taken from each patient immediately before and after PTCA, after 24 h, 1 month and 6 months (samples (0), (1), (2), (3) and (4) respectively)and PF(iu/ml),BTG(iu/ml) and TM(ng/ml)were estimated.

Statistical analysis with ANOVA was performed, using STATISTICA package.

Results: There were no statistically significant differences in basic characteristics and in the values of all 3 substances before PTCA between group-1 and group-2.

Significant Differences

	PF(3)	BTG(2)	BTG(3)	BTG(4)	TM(1)	TM(2)	TM(3)
GROUP-1	86.7±21	220.4±13	218.3±22	222.9±13	27.7±5	29.3±6	29.6±6
GROUP-2	96.9±10	231.7±12	230.9±6	230.8±9	23.6±4	22.9±6	23.4
F	4.85	11.49	7.63	6.59	11.6	15.89	17.26
p	0.031	0.001	0.007	0.012	0.001	0.000	0.000

Conclusions: Oral L-Arginine favorably affects plasma levels of forth Platelet Factor, Thromboglobulin and Thrombomodulin in male pts undergoing elective PTCA, suggesting a protective role against acute or subacute thrombosis and restenosis.

P1205 Point-of-care measurement of platelet function before angioplasty strongly predicts early MACE and late TVR

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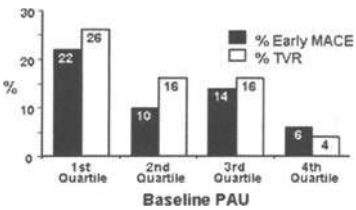
Baseline platelet activation correlates with early thrombotic complications of PCI as well as the need for TVR but is of limited clinical utility due to the need for specialized testing. The Ultegra-RPFA is a simple, point-of-care assay approved for use in monitoring platelet function in patients treated with GPIIb/IIIa antagonists that also quantifies the patient's baseline platelet function.

Method: As part of the GOLD study, baseline Platelet Activation Units (PAU) were measured using the Ultegra-RPFA in 500 patients undergoing a percutaneous coronary intervention with the adjunctive use of a GPIIb/IIIa antagonist. Complete data out to 7 months were available in a subset of 197 abciximab-treated patients, with the incidence of early MACE (death, MI, urgent TVR) and late TVR analyzed with respect to baseline platelet function.

Results: Baseline platelet function ranged from 52 to 471 PAU (median 234). Patients with the lowest PAU values at baseline, consistent with more activated or "exhausted" platelets, had a significantly greater risk of early MACE, as well as late TVR, than those paitents with highest baseline PAU levels (figure).



Relationship of PAU to MACE and TVR.

Conclusion: These results confirm that increased levels of platelet activation prior to PCI are associated with an increased risk of both early MACE and clinical restenosis, and confirm that this can now be easily determined utilizing a simple point-of-care assay. Routine platelet function monitoring may help to optimize the future use of more expensive therapies designed to minimize MACE or prevent restenosis.

P1206 Platelet activation induced by acute coronary thrombosis and transient occlusion is related to an increased risk of early reocclusion

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Platelet activation and circulating platelet-leukocyte aggregates have been described during acute coronary syndromes and may have prognostic significance. It is uncertain to what extent the increased platelet activation in these patients reflects a baseline status or is a consequence of the acute coronary event. In the present study, we investigated the changes in platelet activation induced by acute coronary thrombosis and transient occlusion, and their association with early coronary reocclusion in swine.

Methods: Twelve thiopental-anesthetized, open-chest Large-White pigs were subjected to catheter-induced coronary injury followed by a 48-min occlusion and two hours of reperfusion. Coronary blood flow was continuously monitored with a transit time flow meter. Five animals had coronary reocclusion (four during the first 30 min of reflow). Femoral venous blood was obtained at several time points of the experiment, the expression of P-selectin by platelets and granulocytes was assessed by flow cytometric analysis, and its association with the occurrence of reocclusion investigated.

Results: At baseline, the percentage of P-selectin-positive cells was low, and similar in animals with and without reocclusion. Platelet activation occurred during the experiment, and the levels were directly associated with the occurrence of reocclusion (table). The higher percentage of P-selectin-positive granulocytes in animals with reocclusion remained significant (P=0.016) after adjusting for the effect of time.

	PLA+			GR+		
	baseline	15 min R	90 min R	baseline	15 min R	90 min R
No reocclusion	2.4 (0.5)	2.6 (0.5)	2.5 (0.5)	1.7 (0.5)	3.3 (0.9)	6.0 (1.3)
Reocclusion	3.7 (0.6)	3.0 (0.4)	4.6 (0.6)*	2.2 (0.8)	10.4 (3.9)	19.9 (7.5)*

PLA+ and GR+, percentages (SE) of platelets and granulocytes, respectively, positive for P-selectin; R, reperfusion; *P<0.05 with respect to animals without reocclusion.

Thus, acute coronary thrombosis with transient occlusion promotes platelet activation. Higher levels of platelet activation are associated with early coronary reocclusion, suggesting a cause-effect relationship.

P1207 Evaluation of the role of COX-1 and COX-2 in prostacyclin production in the perfused senescent rat heart

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Background and Objectives: The impaired production of nitric oxide plays a pivotal role in aging-related endothelial dysfunction. In contrast, we have recently reported that the production of prostacyclin is increased in the aged rat heart. We also reported that COX-1 was increased, while prostacyclin receptor expression was not significantly changed. However, involvement of COX-2 in the increased prostacyclin production is not clarified yet. In the pathologic conditions such as inflammation and endotoxin shock, induced COX-2 may play an important role. Therefore, we tried to evaluate the role of COX-2 as well as COX-1 in the age-related changes in prostacyclin production.

Methods: Young (2-3 months old) and senescent (27-30 months old) male Fischer 344 rats were used. Hearts were isolated and Langendorff-perfused with constant pressure (75 cm H2O) at 37°C. Coronary flow, heart rate, left ventricular pressure and its first derivatives were measured. Prostacyclin was measured with the coronary effluent by enzyme-immunoassay for 6-keto PGF1alpha. Gene expressions of COX-1 and COX-2 were quantitated by real-time RT-PCR. Expressions of COX-1 and COX-2 enzymes were analyzed by Western blot. Localization of COX proteins were investigated in tissue sections immunohistochemically.

Results: Endothelin-1 induced a potent vasoconstriction and increased the prostacyclin production. The production was greater in senescent than young rat. Pretreatment with non-selective COX inhibitor diclofenac and selective COX-1 inhibitor resveratrol inhibited the response. On the other hand, selective COX-2 inhibitors (nimesulide and NS-398) did not significantly attenuate the prostacyclin production. Gene expression of COX-1 and prostacyclin synthase mRNA was significantly higher in senescent aorta, while COX-2 mRNA did not show significant change. Western blot analysis revealed that COX-1 expression was upregulated in the senescent aorta, but the level of COX-2 was not changed. Immunohistochemical analysis showed that COX-1 immunoreactivity localized in the coronary artery and aorta was stronger in the senescent rat, but COX-2 expression was faint even in the senescent rat.

Conclusion: These results suggest that COX-1 was involved in the increased production of prostacyclin in the senescent rat heart. However, COX-2 did not seem to play an regulatory role for prostacyclin production in the aging-process.

P1208 Psychological stress induces acute increases in monocyte-platelet, neutrophil-platelet and leukocyte-platelet aggregates in healthy men

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Background: Circulating monocyte-platelet and neutrophil-platelet aggregates have emerged as sensitive markers of in vivo platelet activation. We assessed the impact of acute psychological stress on monocyte-platelet, neutrophil-platelet. Lymphocyte-platelet and total leukocyte-platelet aggregates in healthy men.
Methods: Participants were 36 healthy nonsmoking men aged 30-59 years. Psychological stress was induced by performance of two challenging behavioural tasks (colour-word interference and mirror tracing). Blood was drawn at baseline, immediately following tasks, and at 30 and 75 minutes post-stress, and aggregates were analysed using flow cytometry. Results are expressed as the proportion of each cell type aggregated to platelets. Cardiovascular and subjective stress responses were also monitored.
Results: There were significant increases following stress in monocyte-platelet, neutrophil-platelet, lymphocyte-platelet and total leukocyte-platelet aggregates (table). Note that the leukocyte-platelet value is not equal to the sum of the aggregates of leukocyte subsets, since cell types vary in prevalence. The highest levels of aggregates were not recorded immediately post-stress, but 30 min later, and values had returned to baseline by 75 min. The increase in neutrophil-platelet and leukocyte-platelet aggregates correlated with the stress-induced increase in systolic blood pressure ($r = 0.43$ and 0.38, $P < 0.025$). The increase in monocyte-platelet and neutrophil-platelet aggregates correlated with subjective stress ratings at 30 min ($r = 0.36$ and 0.35, $P < 0.05$).

	Baseline	Post-stress	30 min	75 min
Leukocyte-platelet aggregates (%)	5.26 ± 1.3	5.45 ± 1.3	6.95 ± 2.0*	5.18 ± 1.3
Monocyte-platelet aggregates (%)	9.94 ± 3.7	10.5 ± 3.1	12.4 ± 7.5*	9.72 ± 3.8
Neutrophil-platelet aggregates (%)	4.37 ± 1.1	4.43 ± 1.3	5.10 ± 1.9*	4.79 ± 1.8
Lymphocyte-platelet aggregates (%)	3.38 ± 0.7	3.58 ± 0.9	3.59 ± 0.9*	3.49 ± 0.8

Means and standard deviations* = Different from baseline ($p < 0.05$ - 0.005)

Conclusions: Psychological stress induces platelet activation as indexed by leukocyte-platelet aggregates, with average increases of 24.7% (monocyte-platelet), 16.7% (neutrophil-platelet), 6.6% (lymphocyte-platelet) and 13.2% (total leukocyte-platelet). Platelet activation correlated with cardiovascular and subjective stress reactions, suggesting that sympathoadrenal responses may be responsible.

P1209 Degree of C-reactive protein elevation in coronary angioplasty patients

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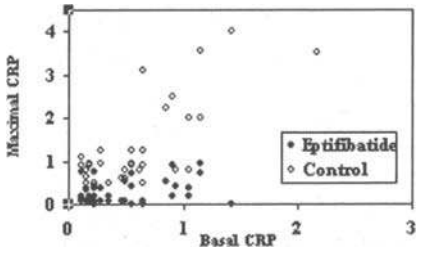
Background: High C-reactive protein (CRP) in coronary angioplasty (CA) patients is a marker of adverse outcome. Some data pointed out that patients with high basal CRP concentration (>0.3 mg/dL) show a significant increase after CA, while patients with low basal CRP levels (<0.3 mg/dL) have no increase at all. GP IIb-IIIa inhibitors block the increase in CRP after CA probably by stabilizing arterial thrombosis. Thus, it would be of great interest to know the expected increase in CRP after CA in order to have a marker of stabilization of the thrombotic conditions.
Methods: We measured CRP levels by nephelometry in 90 patients who underwent a CA. Patients with recent myocardial infarction, recent surgery or inflammatory, metabolic or neoplastic diseases were excluded. In 48 patients Eptifibatide perfusion was initiated immediately after the procedure, and continued for 24 hours. The remaining control 42 patients received only standard heparin plus aspirin treatment. C-reactive protein was determined pre angioplasty, 24 and 48 hours after the procedure.
Results: Linear regression equation for CRP was maximal CRP = 26.45 + 1.74 * (basal CRP) for control patients, and maximal CRP = -0.77 + 1.03 * (basal CRP) for Eptifibatide patients. The figure shows the actual data.



CRP in coronary angioplasty.

Conclusions: C-reactive protein increases in a linear way after CA to almost twice the basal levels, no matter which are that basal concentrations. Eptifibatide blocked that increase, mantaining CRP at basal levels.

P1210 C-reactive protein predicts platelet reactivity and von Willebrand factor expression in patients undergoing coronary stent implantation

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Background: Early after PCI, thrombotic risk is the result of a complex interplay among blood components such as platelets, coagulation and inflammatory factors. The adhesion molecule P-selectin is expressed on the surface of activated platelets and mediates interaction between platelets and leucocytes. Von Willebrand Factor (vWF), a coagulation factor promoting thrombus formation, is involved in signal transduction pathways leading to platelet release reactions. C-reactive protein (CRP) has been associated with a greater risk of restenosis following PCI. Aim of the study was to assess whether CRP is associated with P-selectin expression and with vWF plasma levels in pts undergoing coronary stent implantation (STI)
Methods: We studied 32 consecutive pts undergoing STI. All pts were on treatment with aspirin (100 mg/day) and received a 300 mg loading-dose of clopidogrel at intervention time. During intervention, 100 IU/kg of heparin was administered. Pts receiving GP IIb/IIIa inhibitors were excluded. CRP levels were measured with an ultra sensitive nephelometric method at baseline. Platelet surface P-selectin (CD62-PE) was measured in non-stimulated platelets and after stimulation with 2 μM ADP and 50 μM TRAP using whole blood flow cytometry at baseline and 10 minutes, 1 hour, 4 hours, and 24 hours following STI. vWF was measured at baseline by ELISA. Pts were divided into two groups according to CRP levels: G1 (CRP<10mg/L) and G2 (CRP>10mg/L).
Results (mean±SD): G1 and G2 were composed of 24 (21 males; age:61±9y) and 8 (7 males; age:64±12y) pts, respectively. No difference in P-selectin expression in non-stimulated platelets and in platelets stimulated with ADP was observed between G1 and G2 at any time point. Following challenge with TRAP, P-selectin expression was significantly higher in G2 than in G1 at baseline (94,23±1,9% vs 91,08±6,3%; p=0.041), 10 minutes after STI (93,75±1,1% vs 86,50±14,6%; p=0.024), 1 hour after STI, (94,17±2,2% vs 86,57±16,8%; p=0,041), 4 hours after STI (94,17±3,0% vs 86,79±14,5%; p=0.027), and 24 hours after STI (93,31±2,5% vs 86,73±13,2%; p=0.029). vWF plasma levels were greater in G2 than G1 (188,64±33,8% vs 149,20±41,7%; p=0.022). No difference in platelet count was observed between the two groups.
Conclusion: Patients undergoing STI with elevated CRP levels have a greater platelet expression of P-selectin following TRAP stimuli in vitro and higher levels of vWF. A greater platelet reactivity and a greater expression of coagulation factors may be adjunctive mechanisms by which inflammation may contribute to outcome.

P1211 Age-related difference in lipid and thrombogenic factors in postinfarction patients

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This study aimed to determine the influence of age on levels of lipid and thrombogenic factors in patients after myocardial infarction (MI).

Methods: Blood levels of cholesterol, apolipoprotein A-1, apolipoprotein B, lipoprotein(a), triglycerides, high-density lipoprotein, low density lipoprotein cholesterol, insulin, fibrinogen, von Willebrand factor, factor VII and VIIa, plasminogen activator inhibitor 1, and D-dimer, were measured 2 months after MI in 1045 patients divided into terciles by age categories: <= 53 years (n=358), 54-64 years (n=340) and => 64 years (n=346). Nonfatal MI or cardiac death occurring during a mean 2-year follow-up were considered as an endpoint of the study.

Results: In comparison to older patients, younger patients (< 53 years) had significantly higher levels of triglycerides, cholesterol/HDL ratio, apoB/apoA ratio and insulin and lower levels of Apo-A and HDL cholesterol. Also, body mass index was significantly higher in younger than older patient (29±6, 28±5, and 27±5, respectively; p<0.001). The elderly patients (> 65) had significantly higher levels of fibrinogen, von Willebrand factor, and D-Dimer and significantly lower PAI-1 levels than younger groups. During a mean 26-month follow-up recurrent cardiac events occurred with similar frequency (7%, 8% and 8%, respectively).

Lipid and Thrombogenic Factors by Age

	Age < 53 (n=358)	Age 54-64 (n=340)	Age > 64 (n=346)	p value
Triglycerides (mg/dl)	224 (132)	199 (115)	179(97)	< 0.001
ApoA (mg/dl)	115 (24)	120 (26)	121 (26)	0.017
HDL (mg/dl)	37 (11)	39 (12)	41 (12)	<0.001
Insulin (IU/ml)	21 (36)	20 (24)	17 (24)	0.001
vWF (U/dl)	129 (60)	151 (70)	167 (72)	0.001
Fibrinogen (mg/dl)	338 (89)	354 (87)	366 (87)	0.001
PAI-1 (ng/ml)	33 (34)	27 (26)	25 (21)	<0.001
D-dimer (ng/ml)	348 (413)	450 (355)	773 (910)	<0.001

Values in parentheses are standard deviations

Conclusion: Younger post-MI patients have higher incidence of metabolic syndrome X (increased BMI, triglycerides, insulin, PAI-1 and decreased Apo-A1 and HDL cholesterol) while the older post-MI patients have higher incidence of procoagulant state (increased vVF, fibrinogen, and D-Dimer) leading to a similar risk of recurrent cardiac events.

P1212 Microvascular reactivity in patients with hypercholesterolemia: effect of atorvastatin treatment

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Impaired NO-dependent vasodilation of resistance vessels is an early marker of increased risk of atherosclerosis; utility of the examination of microvasculature, however, is far less established. We have therefore tested the hypothesis that hypercholesterolemia is associated with impaired microvascular reactivity and that this defect is at least partially reversible by lipid-lowering treatment. Methods: Twenty six hypercholesterolemic patients (otherwise healthy, total cholesterol >7,0 mmol/l) were examined at baseline and after 10 wks of atorvastatin treatment (20 mg/day). Skin microvascular reactivity (MR) was examined by laser-doppler flowmetry. Baseline MR values of the study group were compared to control group of healthy subjects, to patients with severe CAD and to patients with diabetes mellitus with and without diabetic retinopathy. Results: Reductions of total cholesterol and LDL-cholesterol after atorvastatin treatment were 31% and 40%, respectively. In the whole treatment group, there was no effect of atorvastatin on MR; however, marked improvement was evident in a subgroup with impaired MR at baseline (+27%, p<0,05). On-treatment changes in MR did not correlate with changes in cholesterol levels. Comparison of baseline values of our study group to those in other patient groups revealed that: 1) MR was normal in subjects with hypercholesterolemia; on the contrary, in patients with severe CAD, MR was substantially impaired (-26%, p<0,05). 2) Similarly, MR was nearly normal in diabetes patients without complications (-8%) but it was impaired in those with retinopathy (-39%, p<0,01). Conclusion: Hypercholesterolemia without symptomatic vascular disease was not associated with impairment of microvascular reactivity; marked decrease of MR was evident only in subjects with hyperlipidemia and severe CAD. Beneficial effect of atorvastatin on MR was limited to the subgroup of patients with impaired MR and this effect was independent of lipid lowering. These results indicate that microvascular reactivity reflects changes of vascular function which appear later in the process of atherogenesis. Supported by grants IGA grants NB 6134-3/200, NB 5986-3/2000 and research project J 13/98 11110000 2-1.

P1213 Preventing microinfarctions with intracoronary nicorandil during percutaneous coronary interventions

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Objective: Impact of rise in creatine phosphokinase (CPK-MB) levels by more than two times the baseline levels following percutneous coronary interventions (PCI) on long term prognosis is now well accepted. The postulate of this study was, dilation of epicardial arteries and the coronary microcirculation with local delivery of nicorandil, a potassium channel opener with vasodilatory properties, could reduce the extent of microembolizations during PCI. We studied the role of intracoronary injection of nicorandil in reducing the level of rise in CPK-MB levels following PCI.

Methods and results: Between April 2000 and September 2001, 45 patients were randomized to intracoronary nicorandil (1mg bolus, Group I), 55 patients to intracoronary nitroglycerin (1mg bolus, Group II), and 50 patients to neither of these drugs (Group III). Patients with acute myocardial infarction and unstable angina were excluded from this study. Baseline clinical characteristics were comparable in all three groups. Multivessel disease was treated in 6.7% patients in Group I, 10.9% pts in Group II and 12% pts in Group III (p=ns). Stenting was employed in 83.3% in Group I, 81.2% in Group II and 85.7% in Group III (p=ns). The incidence of rise in CPK-MB levels more than two times the baseline level in Group II and Group III was statistically more than that occurring in Group I (p=0.03 between Group I and Group II; p= 0.0002 between Group I and Group III). The difference in the mean levels of CPK-MB between Group I (Nicorandil) and Group III (none) was statistically significant (p=0.04).

Creatinephosphokinase MB levels

	CKMB<2 times baseline	CKMB>2 times baseline	Mean CK-MB rise (IU)
Group I (N=45)	43 (95.6)	2(4.4)	14±11
Group II (N=55)	45(81.8)	10(18.2)	26±14
Group III (N=50)	32(64)	18(36)	32±13

Figures in parenthesis indicate percentages

Conclusion: Intracoronary injection of nicorandil reduces the level of rise in CK-MB levels following percutaneous coronary interventions. Follow up of these cases will give us information about its impact on long term adverse effect rate.

P1214 Effective treatment of stable CAD by atorvastatin guided by noninvasive PET assessment of regional myocardial perfusion

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Noninvasive dipyridamole (D) positron emission tomography (PET) reflects the integrated flow capacity of the coronary arterial/arteriolar system affected by diffuse atherosclerosis, often the substrate for plaque rupture. We examined the effect of atorvastatin in stable CAD on myocardial perfusion in regions with highest reduction of baseline dilator reserve. 13 patients (Pts.) with mild effort and/or atypical angina (AP) and hypercholesterolemia were studied before and after 5±1.7 months of therapy with 10-80 mg atorvastatin. Exclusion criteria were smoking, diabetes, uncontrolled hypertension, and pre-treatment with lipid lowering drugs.

Baseline data: Mean age:63.7±5.8 years; nine of the patients (9 men;4 women) had mild coronary artery disease (wall irregularities or stenosis <= 50%), four had multi-vessel disease (stenosis>70%).

Methods: Dynamic PET flow was measured quantitatively at rest (MBFR) and after D (0.56 mg/kg) (MBFD) using N-13 ammonia as flow tracer in a 3-compartment model. Pts. had restricted flow reserve (CFR) compared to normolipemic controls (n=15; 52±11 years; overall CFR: 4.0±1.3; p<0.01). Chol.: 271±25; LDL-C: 197±21; HDL: 50±9 mg/dl; CFR: 2.1±0.48; minimum coronary resistance (MR) was calculated as mean arterial pressure/MBFD; conductance as 1/MR.

Results (mean±SD): Chol:176±43; LDL-C:101±28 (-49%); HDL:51±11 mg/dl. Regional MBFD increased from 164±40 to 217±46 ml/min x 100g (p<0.05); MR decreased from 0.62±0.15 to 0.47±0.09 mmHg/ml/min x 100g (p<0.02). Regional coronary conductance ratio increased from 1.74±0.5 to 2.24±0.53 (p<0.02). Clinical improvement was reported by 12/13 (92%) and complete relief of symptoms by 7/13 (54%).

Conclusions: Even after a short treatment period, atorvastatin significantly improves regional myocardial perfusion, substantially restricted at baseline, with concomitant improvement of anginal symptoms. These data support the noninvasive management of stable CAD with statins guided by PET.

P1215 The β-blocker therapy improves the increased mortality in African-Americans with coronary heart disease treated with calcium channel blockers

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Introduction: Calcium channel blockers (CCB) are widely used in African-Americans (AA) for the treatment of hypertension and coronary heart disease (CHD).This preference is mostly based on favorable antihypertensive effects. Studies in mostly caucasian patients(pts) suggest adverse effects with CCB on cardiovascular outcomes. The effects of CCB and the combination with b-blockers (BB) on outcomes in AA,have not been carefully studied.
Methods: We studied the interaction of treatment on mortality rates in 812 AA men (68±10yrs),who underwent diagnostic cardiac catheterization, echocardiogram, Holter ECG monitoring,exercise treadmill test and blood chemistry. Of these pts,309 were treated with CCB, 87 with BB,151 with both (CCB+BB) and 265 were on neither BB or CCB. Among pts treated with CCB,141 were on Nifedipine, 234 on Diltiazem, 38 on Verapamil, 41 on Amlodipine and 8 on Felodipine.
Results: Compared to pts on no CCB,pts treated with CCB had more favorale ejection fraction (58±16 vs 54±17;p<0.001).There were no other differences between pts (age,BMI,LVMI,SBP,DBP). Over a period of 10 years (120±28 months) a total 286 deaths occurred. Mortality rates were higher in pts receiving CCB (RR=1.97;CI=1.5-2.5;p=0.000). When CCB were combined with BB the risk was lower than CCB alone (p=0.0001). Subgroup analysis revealed that most of the increased mortality was due to Nifedipine (58% vs 23%;OR:4.4;p<0.000),after adjusting for confounding factors including severity of CHD. When Nifedipine was combined with BB the risk was lower than Nifedipine alone (p=0.001). There was no statistical difference in pts with Diltiazem (28.8% vs 29.1%),Verapamil and Felodipine. The combination of Diltiazem with BB had a lower risk than Diltiazem alone (p=0.03). Amlodipine had a "favorable" effect (4.8% vs 30%) in mortality rates.
Conclusion: In AA with CHD treatment with Nifedipine identifies a population in extremely high risk for cardiovascular events. Treatment with other types of CCB has no adverse effect.
The combination of BB with CCB has a beneficial effect reducing the mortality rates in this population.

MYOCARDIAL INFARCTION – INSIGHTS TO PATHOPHYSIOLOGY

P1216 Preinfarction angina may preserve the myocardial microcirculation and function after revascularization

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Objective: To assess the influence of preinfarction angina upon the myocardial microcirculation and cardiac function after revascularization using intravenous myocardial contrast echocardiography (MCE). Methods: Twenty-nine patients with acute myocardial infarction (AMI) were studied by means of MCE. 8.5ml of Levovist (300mg/ml) was injected intravenously 3-4ml per minute as contrast media. Harmonic power Doppler (Philips Sonos 5500) was used for myocardial imaging one week after successful revascularization. Twenty patients had PTCA plus stent, 8 had CABG, and 1 had PTCA plus stent followed by CABG within 23.6±3.6 days after the onset of AMI. All patients had TIMI grade 3 flow after PTCA plus stent. Seventeen patients (Group A) had at least one episode of angina within one week before infarction, and 12 (Group B) did not. Results: The incidence of no flow (myocardial contrast score index <0.5) was lower in Group A than in Group B patients (17.6% vs. 66.7%, p<0.05). The end-diastolic dimension (EDD) was not significantly different in Group A and Group B in the first week after revascularization (52.23±6.53mm, 55.02±9.49mm, p>0.05). It, however, decreased significantly in the fifth week after revascularization in Group A patients (47.36±5.56mm vs. 52.23±6.53mm, p<0.05), but was not changed in Group B patients (55.47±8.38mm vs. 55.02±9.49mm, p>0.05). The left ventricular ejection fraction (EF) was found to be improved in Group A patients (39.42% verse 34.61%, p<0.05), while it was not changed in Group B patients (28.33% vs. 29.22%, p>0.05). Conclusions: Preinfarction angina may preserve myocardial microcirculation and cardiac function, may help to improve the left ventricular remodeling as well.

P1217 Platelet/endothelial activation in depressed patients after acute myocardial infarction and unstable angina: evidence from clinical trials

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Background: Platelets play a key role in the progression of acute cardiovascular syndromes (ACS). Clinical depression is also associated with enhanced platelet function. The purpose of this study was to assess concentrations of platelet/endothelial biomarkers in patients with acute myocardial infarction (AMI), and unstable angina (UA) enrolled in the clinical trials, dependent on the incidence of depression, and to compare these data with those of healthy controls.
Methods: Two hundred eighty one baseline plasma sample (AMI=41 (ASSENT-2); UA=126 (PRONTO); depression after ACS=64 (SADHART), and controls=50) were analyzed. Blood was drawn before applying any therapeutic strategies including interventions, thrombolytics, infusions, selective serotonin reuptake inhibitors, etc. Platelet factor 4 (PF4), beta-thromboglobulin (beta-TG), platelet/endothelial cell adhesion molecule-1 (PECAM-1), P-selectin, thromboxane (TxB2), prostacyclin (6-keto-PGF1a), vascular cell adhesion molecule–1 (VCAM-1), and E-selectin were measured by ELISA.
Results: Patients with ACS exhibited higher degree of platelet activation than controls independently of the incidence of depression. Plasma levels of P-selectin, TxB2, 6-keto-PGF1a, and VCAM-1 were higher in AMI group when compared with both depressed and non-depressed population with ACS. Surprisingly, depressed post-ACS patients exhibited the highest levels of PF4, beta-TG, and PECAM-1 when compared with the AMI and UA groups. E-selectin plasma level was constantly elevated, but did not differ among the groups. Depressed post-ACS group had higher plasma levels of all biomarkers as compared to the non-depressed UA patients.
Conclusion: Retrospective analysis of the data from several clinical trials reveals that depression indeed contributes to the hightened platelet activity in post-AMI, and/or UA patients, suggesting more aggressive anti-platelet strategy in patients with mood disorders after ACS.

P1218 Matrix metalloproteinases activity in acute myocardial infarction patients. Do their activity contributed to post-myocardial infarction dilation?

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Matrix Metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are key enzymes in myocardial fibrillar collagen degradation. Do the increased activity of them as expressed by their plasma levels in patients (pts) with acute myocardial infarction (AMI) contribute to the post-MI remodeling?
Methods: Plasma levels of MMP-1, TIMP-1 and complex MMP-1/TIMP-1 (Comp) were measured in 24 AMI pts mean age (58,46+_13,9) years. Blood samples were taken on admission (0h), 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 3 day, 4d, 5d, 7d, 15d and 30 days there after and measured by relevant ELISA kits.Coronary arteriography, LV-venticulography and a two-D Echocardiography were done for estimation of Ejection Fraction (EF), diseased vessels, and LV-End Diastolic-Diameter (EDD). Pts (n=10) with EF <45%, EDD>47,5 mm and third Heart Sound (S3) were included in group (A) and compared to 12 pts consisting the group (B) with EF>45%, EDD <47,5 mm and without S3. Pts suffered from any other disease were excluded. ANOVA rp.m.a and unpaired t-test were used for statistical analysis. Data expressed as mean values+_ SD in ng/ml p<0,05 was consisted statistically significant.
Results: Group A pts showed higher levels of MMP-1 lower levels of TIMP-1 and Comp activity follow up by higher EDD and lower EF compared to group B pts showing lower levels of MMP-1 and TIMP-1 and higher level of Comp activity, lower EDD and higher EF. Additionally on 6h, 18h, 24h, 48h, for MMP-1 and 48h and 4 day for Comp the difference of mean values between group A and B was statistically significant from p>0,007 to p<0,025.

	Group A	Group B	Difference (%)
MMP-1 (ng/ml)	1,31± 0,69	1± 0,52	+ 24
TIMP-1 (ng/ml)	704,2± 899,5	697,1± 507,2	+1
Comp (ng/ml)	2,65± 2,15	3,67± 1,95	- 38
EF%	35,8±8,85	51,25±1,8	- 43
EDD (mm)	52,19±6,99	42,97±3,22	+17

Conclusions: Thus the degree of collagenolysis in AMI pts as expressed by higher MMP-1 and lower TIMP-1 and Comp activity followed by higher EDD and lower EF may be related to the post-MI dilation and to late process of LV remodeling.

P1219 The morning peak of acute myocardial infarction's onset is caused by patients with sleep apnea syndrome

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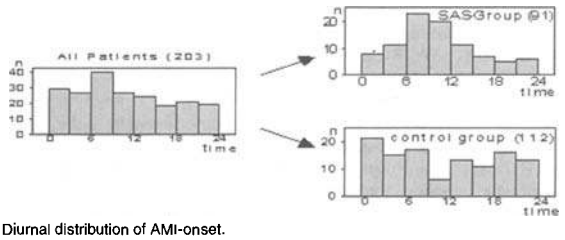
Is there a relation between the circadian rhythm of acute myocardial infarction (AMI) in the morning hours and the sleep apnea syndrome (SAS)?
Method: 203 patients after AMI (7.-14.day) were examined for sleep associated breathing disorders by means of a 5-channel recording system. Patients with congestive heart failure were excluded, all patients were mobile. The diagnostic criterion for SAS was > 10 episodes of apnea and hypopnea/h (AHI>10).
Results: SAS was diagnosed in 44,8% of all AMI patients (91/203 patients). Compared to the 112 patients without SAS there were significantly more AMI in the morning hours (6:00am-12:00am) in the SAS-group (49,5%) than in the non-SAS group (21,4%). Chi-Square-Test: p<0,0001. Patients with SAS differed from non-SAS patients only in the symptom of daytime sleepiness (29,7% vs 17,0%), age (mean 64,6years vs 60,2years) and were less likely to be smokers (33,0% vs 51,8%). There were no significant differences between SAS- and non-SAS group for BMI (mean 27,4 vs 27,1), hypertension (70,3% vs 61,6%), hyperlipoproteinemia (53,8% vs 50,9%), diabetes mellitus (19,8% vs 18,8%), family case history (20,9% vs 33,0%), history of cardiovascular disease (28,6% vs 21,4%) and the taking of sedatives (16,7% vs 21,4%).



Diurnal distribution of AMI-onset.

The strong association between SAS and morning onset of AMI could be caused by sympathetic stress reactions in consequence of the breathing disorder.

P1220 Left ventricle mechanical asynchrony in patients with acute myocardial infarction

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Background: Remodeling post myocardial infarction is an important process that leads to progressive ventricular enlargement and heart failure. It is not clear what impact an area of infarction will have on electrical synchrony of the whole ventricle. Therefore, we have assessed the degree of LV synchrony of the whole LV post myocardial infarction using tissue Doppler imaging (TDI).
Methods: Standard echocardiography and TDI were performed in 27 healthy volunteers (age 60.96±12.49) and 39 AMI patients (age59.56±11.39) within 1~7 days at the apical 2 and 4- chamber views, interrogating the following segments: septal, lateral, anterior and inferior segments at annulus, basal, mid and apical levels, and the following parameters were measured: the time to peak IVC, IVCT, the time to peak systole and systolic duration. MRI was performed in all AMI patients to assess the site and extent of the infarction.
Results: All the patient had a normal QRS duration. There was a significantly higher prevalence of prolonged time to peak systole in the whole LV in the patient group compared to normal (20.5% Vs 3.7%) (p=0.05), and it was even higher in the anterior AMI subgroup compared to normal (28.6% Vs 3.7%) (p=0.002). The ejection time was significantly prolonged in the annulus, basal, mid and most of the apical segments in patient group when compared to controls (p<0.05). Furthermore, in anterior MI subgroup the time to peak IVC was prolonged in lateral wall (p=0.01), and the time to peak systole was prolonged in anterior wall (p=0.03) compared to normal, whereas the systolic time was shortened in septum (p=0.015). In inferior MI subgroup the systolic time was shortened in septum (p=0.03) and inferior wall (p=0.029) compared to normal.
Conclusions: Myocardial infarction has a significant impact on left ventricular synchronization early after the infarction even in the absence of bundle branch block.

P1221 Baseline oxigen saturation obtained by pulse-oximetry and diagnosis of heart failure in the acute phase of myocardial infarction

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The continuous monitoring of oxygen saturation (SaO2) by pulse oximetry is a current practice in many coronary care units in patients with acute myocardial infarction (AMI), but its correlation with cardiac failure (CF) has not been established.
Methods: With this objective, 206 consecutive patients with AMI were prospectively studied in the morning round for the first three days, registering simultaneous daily data from physical examination (Killip classification), chest x-ray film (Battler score evaluated by two observers) and baseline SaO2 (measured when patients were breathing room air or taking the steadiest value after a short discontinuation of oxygen therapy). The latter was also obtained at every nursing turn. Patients with cardiogenic shock (Killip IV) were excluded.
Results: 610 simultaneous registries were obtained: Killip I (66%), Killip II (21%) and Killip III (12%). There was a good correlation between baseline SaO2 and physical examination (Killip/SaO2) (mean ± SD): I/ 94 ±1.9%, II/ 91±2.6% and III/ 84±8% (R= -0.66, p<0.001) and with x-ray film (Battler/SaO2): 0/ 94±1.7%, 1/ 93±2.4%, 2/ 90±3.9%, 3/ 89±4%, 4/ 81±9% (R=-0.65, p<0.001) although a better correlation was found between Killip and Battler scores (R= 0.84). Left ventricular ejection fraction also correlated with the worst Killip, Battler and SaO2 (R=-0.56, -0.57 and -0.412; p<0.001 respectively). True CF was defined by the association of Battler >1 and Killip >1. ROC curves showed SaO2 < 93% to be the cutoff with greater area under the curve, showing a sensitivity of 76%, specificity of 86% and test accuracy of 86%.
Conclusion: Baseline SaO2 determination by pulse oximetry is a useful tool to identify cardiac failure in patients with AMI and may be an early sign of this complication if values are below 93%. Baseline SaO2 must be considered in the routine evaluation of these patients.

P1222 Hepatocyte growth factor: the advent of a unique angiogenic marker for the early detection of acute myocardial infarction patients

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Hepatocyte growth factor (HGF) is a multipotent molecule and a member of the endothelium- specific growth factors transducing a wide range of biological signals, including mitogenesis, motogenesis and morphogenesis, as well as an organotrophic factor for regeneration of various organs exhibiting a potent angiogenic and antiapoptotic activity in several cell types. In the present study we sought to elucidate any possible role of HGF in acute myocardial infarction (AMI) parients.
Methods: We measured serum HGF levels in 24 pts with first attack of AMI, admitted and thrombolysed during the acute phase,and no previous history of any other disease,and compared to those of 20 sex and age- matched normal controls (NC) with mean values: 0,32 ± 0.06 ng/ml. Serum samples were collected at the time of hospital admission (0 hours), as well as 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 3 days, 4d, 5d, 7d, 15d and 30d thereafter and measured by ELISA method.
Results: Data is expressed as mean values ± SEM in ng/ml. For the statistical analysis non- parametric Wilcoxon test was used, with a statistical significance of p<0,05 compared to corresponding values of: a) NC (*), b) the lowest serum value at 36h (°). HGF exhibited significantly high initial serum levels on admission (7,67 ± 2,43 *°) reaching a maximum at 3h (8,75 ± 2,67 *°). A gradual decline followed leading to a nadir at 36h (1,68 ± 0,35),which was succeeded by a steep increase up to a later peak at 4d (5,77 ± 1,84 *°). HGF gradually returned within normal range finally. Furthermore,when classified according to infarct size, pts with extensive AMI and adverse events during the early post-AMI period, exhibited a higher, more sustained initial HGF peak compared to those with minor AMI and uncomplicated clinical course (17,32 ± 4,65 vs 6,44 ± 1,67, p<0,05).
Conclusions: Thus, a statistically significant double- peak increase of HGF serum levels in AMI pts has been observed. The initially 24- fold increased HGF possibly acts as a survival factor against endothelial cell death caused by acute hypoxia due to reduced vascular perfusion, while the following progressive decrease could be attributed to thrombolytic therapy and reperfusion. The raised HGF levels, 4 days later, may be fundamental for the induction of angiogenesis implicated to the process of ventricular remodeling, thus preserving cardiac function. Therefore, HGF seems to be a useful marker for the early detection of AMI pts, as well as a prognostic indicator reflecting their clinical course.

P1223 Cardiac endothelin-1 receptors are increased in the acute phase of myocardial infarction in humans

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Plasma concentration of endothelin-1 (ET-1) are increased in the acute phase of myocardial infarction and experimental studies showed that chronic ET-1 receptor antagonist administration may improve ventricular remodelling and survival. To investigate cardiac ET-1 receptors in acute myocardial infarction we studied cardiac ET-1 receptors in the hearts of 15 patients dead 1 (n=3), 3 (n=4), 7 (n=5) and 20-30 days (n=3) after acute anterolateral myocardial infarction. Only patients who had not received thrombolysis or reperfusion were selected. The control group was formed by age-matched patients dead for noncardiac reasons. ET-1 receptors on isolated cardiac membranes were investigated using binding methods with 125I-ET-1 (2000 Ci/mmol, Amersham) as radiolabeled ligand and ET-1 (0-1μM) as cold displacer. Cardiac specimens were collected at necroscopy performed 24 hours after exitus. Receptor binding stability was preliminarly checked in hearts explanted from patients undergoing cardiac transplantation stored at 15°C for 12, 24 and 48 hours. Preliminary experiments performed on explanted hearts showed only a 21% increase in ET-1 receptor density at 48 h ($p<0.05$). In necroscopy specimens taken in post-AMI patients ET-1 receptor density was slightly decreased at day 1 (-25%, ns vs controls), increased by 82% at 3 days ($p<0.01$) and remained elevated at 30 days (+113%, $p<0.01$). In conclusion, cardiac ET-1 receptors sharply increases during the first week following myocardial infarction and remains elevated during the following month.

P1224 Oxidized low-density lipoprotein in patients with unstable coronary artery disease and a healthy control population

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Background: In the clinical setting of coronary artery disease measurement of serum levels of cholesterol, LDL and HDL is common practice. Oxidatively modified low-density lipoprotein is however receiving considerable attention as evidence is mounting for its pivotal role in the initiation and progression of atherosclerosis. Measurement of oxidized LDL has not found its way into the clinical arena as many methods have been hampered by methodological drawbacks and small patient samples.
Material and methods: Using a recently developed sandwich ELISA method we evaluated the relation of oxidized LDL in 164 patients with unstable coronary artery disease (UCAD) included in the FRISC-II trial and in an equal number of age and gender matched healthy controls. 17,7% of FRISC-II patients were on treatment for hyperlipidemia.
Results: In UCAD patients oxidized LDL levels at admission were significantly higher than in controls ($p<0,001$). Total cholesterol did not differ among groups. HDL was significantly higher ($p<0,001$)and LDL significantly lower in controls ($p=0,007$).

Variable	Controls (n=164)	FRISC II (n=164)	p-value
s-cholesterol (mmol/l)	5.68±0.93	5.61±1.08	n.s.
s-HDL (mmol/l)	1.53±0.40	1.07±0.29	p<0.001
s-LDL (mmol/l)	3.37±0.83	3.62±1.03	p=0.007
s-oxLDL (U/l)	50.37±13.53	77.51±19.81	p<0.001

Conclusion: This study confirms findings in previous studies of elevated levels of oxidized LDL in patients with unstable coronary artery disease compared to healthy controls.

P1225 Tissue factor promotor polymorphisms are associated with an increased risk of myocardial infarction

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The transmembrane glykoprotein tissue factor (TF) is the main initiator of the extrinsic coagulation cascade. TF Expression in atherosclerotic lesions plays an imporant role in local thrombus formation in acute coronary syndromes. Expression levels may be associated with different promoter polymorphisms and thereby contribute to the risk of acute myocardial infarction.
Patients with myocardial infarction (MI, n=793) and age and sex matched patients without coronary artery disease (K=340) were included. After isolation of DNA (QIAamp blood kit, Qiagen, Hilden, Germany) TF promotor polymorphisms -603 A/G and -1322 C/T were analyzed by amplification with allel specific probes (TaqMan). Both polymorphisms were concordant in 99.6% of all patients. In patients with AMI the -603 G (MI: 76%, K: 70%) allel and the -1322 T-allel (MI 76%, K: 70%) were prevalent (P=0,04). Multivariate analysis revealed an odds ratio of 1.44 (confidence intervall 1.07-1.93).
Thus,carriage ot the -603 G and the -1322 T allel is associated with an increased risk für acute myocardial infarction. The relationship between promotor polymorphism and TF Expression requires further investigations.

P1226 Intracoronary enalaprilat reduces postischaemic leukocyte-adhesion and improves coronary blood flow in patients with acute myocardial infarction

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Background: Although reopening of the infarct related artery (IRA) is the established therapy in acute myocardial infarction there is some experimental evidence that reperfusion is associated with a distinct tissue damage. This myocardial injury after ischemia and reperfusion involves postcapillary leukocyte endothelial interactions mediated by cell adhesion molecules, a phenomenon probably aggravated by endothelin-1 (ET-1). Since ACE-inhibition has been shown to be cardioprotective by decreasing leukocyte adhesion and ET-1 release, we investigated the effects of intracoronary (i.c.) enalaprilat, infused during reperfusion in acute myocardial infarction. Methods: Twenty two patients with a large acute myocardial infarction were randomized to receive (i.c.) either enalaprilat (E; 50 μg) or placebo (P) immediately after reopening of the infarct vessel by primary PCI. Plasma concentrations of soluble L-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and ET-1 were measured before PCI and at 2, 10 and 60 min after E or P i.c. in pulmonary arterial blood. Moreover, corrected TIMI frame counts (CTFC) and 10 days follow-up LV-angiography for all patients were assessed.
Results: During reperfusion there was a significant early increase in sL-selectin (+12.7%*), sP-selectin (12,5%*) and ET-1 (+304%*) after P, which was suppressed by E. ICAM-1- and VCAM-1-levels were not affected during reperfusion in both groups. CTFC after primary PCI suggested an increase in myocardial blood flow in the infarct related artery (CTFC E vs. P: 43±7 vs. 81±30; $p=0.07$) and in the reference vessel ($p<0.01$) after E. Moreover, LV-ejection fraction tended to be improved during 10 days follow-up LV-angiography (LVEF E vs. P: +5.1% vs. -0.8%; $p= 0.06$).
Conclusion: Intracoronary enalaprilat prevents postischemic leukocyte adhesion and the release of ET-1 after primary PCI and might therefore be a promising approach to improve coronary blood flow and LV-function after acute myocardial infarction.

P1227 Prompt improvement of the endothelial function by simvastatin in the acute coronary syndrome

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Increasing evidence suggests that starting early statin therapy in patients who suffered an acute coronary syndrome (ACS) is associated with substantial prognostic improvement. The exact mechanism of this benefit is not yet completely understood, but it cannot be explained only on the basis of reduction of plasma cholesterol levels. Many studies indicate that treatment with statins improves the endothelial function and vasomotion.
The aim of our study was to assess the hypothesis that early therapy with Simvastatin in ACS patients (pt) is followed by a rapid improvement of endothelial function. We included 49 patients hospitalized with ACS, with cholesterol values below 200mg/dl at the time of hospitalization. They were randomly assigned to receive Simvastatin 40 mg daily (25pt), after the first 24 hours, or no hypolipemiant drug (24pt). Both groups had similar basal characteristics, including the proportion of unstable angina and acute myocardial infarction; also, the two groups were similar regarding the left ventricular ejection fraction and the treatment for ACS (which included ASA, beta-blockers and ACEI). For both groups we determined at the beginning of the study and after 6 weeks the flow-mediated vasodilatation (FMD) and the endothelium-independent Nitroglycerine vasodilatation (NMD). FMD was defined as percent change in brachial artery diameter at 1 min. after 5 min. of upper arm blood pressure cuff occlusion.
Results: Multiple determinations were made in order to assess FMD (interobserver variability < 1.2%). Basal FMD was not different in the Simvastatin treated pts. and in the not treated pts. (3.1±2.7% vs. 3.3±2.9%, p: NS). Also, basal NMD values were not different in the Simvastatin treated and the not treated pts. At 6 weeks FMD was significantly improved in the Simvastatin treated pts. compared with the not treated pts.: 11.3±0.7% versus 5.33±0.2%, $p<0.03$. NMD was not different between the Simvastatin treated and the not treated pts. (22.9±1.3% vs. 21.5±0.6%, p:NS). At 6 weeks the cholesterol values did not differ significantly vs. basal values and between the Simvastatin treated and the not treated pts.
Conclusion: Simvastatin administered on early bases in ACS normocholesterolemic patients improves promptly the endothelial function as determined by FMD. This effect may contribute to the positive long-term prognostic implications of the use of statins in ACS.

P1228 Ischaemia induces interleukin 6 and tissue factor production in patients with coronary artery disease. A dobutamine stress echocardiograhy study

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Interleukin 6 (IL6) and macrophage colony stimulating factor (MCSF) plasma levels are elevated after acute myocardial infarction. IL6 also mediates the ischemia-reperfusion myocardial injury in experimental models. We investigated whether reversible ischemia induces cytokine production leading to increased tissue factor (TF) expression after dobutamine stress echocardiography (DSE) in patients with stable coronary artery disease (SA).

Methods: Eighty patients with SA were studied by DSE and were compared to 24 normal controls. Blood samples were obtained at rest, at peak stress and 20min after cessation of dobutamine infusion (rec) for measurement (median, 25th-75th percentile) of MCSF, IL6 and TF plasma levels (pg/ml). Patients had angiograpically documented CAD. New or worsening region wall motion abnormalities (RWMA) at stress and their duration in rec were noted.

Results.Patients had higher rest IL6, MCSF and TF than controls ($p<0.01$,Table). During DSE,45 patients presented ischemia. Patients with and without ischemia achieved similar heart-rate product at peak stress. IL6 and TF levels increased at peak stress and at rec compared to rest in ischemic but not in non-ischemic patients (Table, $p<0.05$). MCSF levels were similar at rest, at peak stress and rec in all patients. High MCSF was related with high TF only in ischemic patients in rec ($r=0.61$, $p<0.01$). Patients with RWMA lasting>5 min in rec (n=20) had higher IL6 at stress and rec than those with RWMA lasting <5 min (stress: 3.3 (2.4-4.6) vs 2.0 (1.5-2.7), rec: 2.7 (2.3-4.3) vs 1.9 (1.4-2.7), $p<0.01$).

DSE	Rest-IL6	Stress-IL6	Rec-IL6	Rest-TF	Stress-TF	Rec-TF
Ischemic (n=45)	2.1 (1.5-2.8)	2.5 (1.7-3.3)	2.4 (1.6-3.4)	266 (132-405)	371 (142-576)	385 (141-577)
Non ischemic (n=35)	2.1 (1.3-3.2)	2.1 (1.4-3.5)	2.2 (1.4-3.6)	371 (142-576)	312 (210-590)	328 (265-600)
Controls (n=24)	1.7 (0.5-1.9)			187 (120-220)		

$P<0.01$, peak stress and recovery vs rest in ischemic patients and in patients vs controls

Conclusion: Reversible ischemia induces an increase of IL-6 and TF plasma levels that is sustained in recovery after DSE. MSCF is related to TF plasma levels during the post ischemic period. Increased production of IL6 persisting throughout recovery may explain the persistent left ventricular dysfunction observed in the post-ischemic period after DSE since this cytokine has a direct negative inotropic action.

P1229 Interleukin (IL)-10 and nitric oxide in acute coronary syndromes

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Background: Activities of cytokines with antiinflammatory properties during cardiovascular diseases bacome in the field of interest. Some studies measured IL-10 in the serum at acute myocardial infarction (AMI), stable and unstable angina (UA) patients (pts). IL-10 expression has been revealed in atherosclerotic plaques and was associated with decreased inducible nitric oxide synthase (iNOS) expression. Increased serum nitrite/nitrate were more evident in Il-10-deficient than in wild-type mice during reperfusion.

In our study we measured plasma IL-10 and total nitric oxide (NO) concentrations at the pts with different presentations of acute coronary syndromes (ACS) - UA and AMI.

Methods: 56 pts with ACS were examined - 42 pts with AMI and 14 pts with UA. Blood was taken at admission. Plasma IL-10 concentrations were measured by an enzyme immunoassay (CytElisa, Maryland; sensitivity 1,6 pg/ml). For the quantitative determination of total nitrite concentrations in plasma were used R&D Systems' Total Nitric Oxide Assay (sensitivity less that 1,35 μmol/l) wich involves the conversion of nitrate to nitrite by the enzyme nitrate reductase.

Results: AMI pts had higher IL-10 plasma levels as compared with UA pts (54,39±26,83 pg/ml vs 42,84±22,43 pg/ml; p less 0,001). In pts with Q-wave AMI (35 pts) IL-10 mean concentration were 63,17±39,51 pg/ml, which was higher than in non-Q AMI pts (21 pts) - 45,61±27,19 pg/ml; p less 0,001. Concentrations of total nitrite in plasma of UA pts were 25,37±4,26 μmol/l which statistically higher than in plasma of AMI pts - 14,74±3,28 μmol/l (p less 0,01).

Conclusions: The results suggests that during UA plasma IL-10 concentrations are associated with clinical instability and during periods of myocardial ischemia/reperfusion may be essential for cardioprotection and have a role in healing. Impaired NO production may contribute to the development of more severe presentations of acute coronary syndromes.

P1230 Angiotensin-converting enzyme Immunoreactvity is associated with macrophage-infiltration and cell proliferation in "de-novo" coronary plaques

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Background: Angiotensin-II contributes to the initiation and progression of atherosclerosis while its reduction following angiotensin-converting enzyme (ACE) inhibition may account for the vascular protection provided by these drugs. Therefore, ACE in the plaque is likely to be a substratum for the clinical benefits of ACE-inhibitors. The hypothesis was made that ACE in the atherosclerotic plaque could be involved with inflammation and cell proliferation. **Methods:** Histology and immunocytochemistry of "de-novo" coronary plaques retrieved with directional coronary atherectomy were analyzed in 124 patients: 74 with stable angina, 35 with sub-acute and 15 with acute unstable angina. Statistical analysis was performed on total and segmental stained plaque areas quantified by computer-aided planimetry. **Results:** Compared to stable patients, unstable patients showed more thrombotic lesions (72% versus 27% $p<0.0001$), smaller areas of fibrous type of plaque (2.3±1.2 mm^2 versus 2.8±1.1 mm^2, $p=0.03$), a higher cellular proliferative score assessed with Ki-67 immunostaining (0.78±0.9 versus 0.27±0.6, $p=0.003$), larger content of ACE-immunostained cells (25.4±23 versus 13.2±15%, $p=0.007$) and larger areas of inflammation as identified by KP-1 immunostaining (30±22 versus 21±20%, $p=0.03$). A significant linear correlation was found between KP-1 and ACE stained areas (mm^2) among unstable patients ($r=0.6$, $p=0.0001$) and was absent among stable patients ($r=0.006$, $p=0.9$). Co-localization of ACE and KP-1 was confirmed by double-immunostaining. Patients with ki-67 evidence of cell proliferation had larger contents of ACE (30.3±20% versus 14.5±19%, $p=0.004$). Proliferating cells were found to be mostly inflammatory and in part also spindled-shaped smooth muscle cells. **Conclusions:** ACE immunoactivity is associated with the process of plaque inflammation and cell proliferation in "de-novo" lesions. Both, the total content of ACE and its co-existence with areas of inflammation are significantly larger in patients with unstable angina. These observations support a role of the enzyme in the pathophysiology of plaques responsible for unstable syndromes and suggest potentially different effects of ACE-inhibitors according to clinical presentation.

P1231 Circulating vasoactive amyloid beta protein ending at 42 amino acid is elevated in severe acute myocardial infarction

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Background: Circulating amyloid beta protein ending at 42 amino acid (Abeta42) can induce oxidative stress-mediated loss of vascular endothelial function, as evidenced by increased vasoconstriction and decreased endothlium-dependent vasodilation, in the periphery and the brain, that is distinct from the reporeted neurotoxic effects produced by aggregated forms of Abeta42. Vascular tissues produce Abeta42 in respose to an hypoxic/ischemic stress insult. Moreover Abeta42 is released during platelet activation and degranulation and it may have an important physiological role in events associated with clot formation. Aim of this study was to delineate whether the formation of circulating Abeta42 would be favoured by a severe acute myocardial infarction (AMI). **Methods:** In 21 patients (pts) with first attack of AMI, large infarct size, ejection fraction <45%, no evidence of any later thrombotic occlussion, extension of myocardial necrosis, or any other disease, serum levels of Abeta42 were determined on hospital admission [mean latency from the onset of chest pain: 2±1 hours (h)] before thrombolysis (0h) and after 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 72h, 4 days (d), 5d, 7d, 15d and 30d and compared to corresponding values of 20 age- and sex-matched healthy controls (HS). **Results:** At 0h, Abeta42 levels were noticed to be significantly higher in comparison to the respective levels of HS (26.7±1.1 vs 1.3±0.3 pg/mL, $p=0.001$). After that, a gradual drop of Abeta42 levels to their lowest values at 6h (18.2±7.8 pg/mL) was noticed and followed by a progressive elevation of them to their highest values at 30d (35.9±6.4 pg/mL), (in both cases $p<0.05$ in comparison to the respective levels at 0h). **Conclusions:** In severe AMI, serum levels of Abeta42 are elevated even at the very first 2h from the onset of chest pain, possibly due, primarly, to platelet aggregation relevant to thrombus formation. Since effective thrombolysis appears to reduce Abeta42 serum levels, not only temporally but also partially, in comparison to respective HS serum levels, other Abeta42 sources might be, in the meanwhile, implicated. This is in accordance with the following progressive elevation of Abeta42 levels, possibly due to the long-lasting action of the preceding elevated circulating Abeta42 on the vessel wall, which is well recognized to upregulate Abeta42 production. Since circulating Abeta42 has been shown to interact with and to cross blood-brain barrier, severe AMI-induced elevated circulating Abeta42 may contribute to progress not only in cardiovascular but also in cerebrovascular disorders.

P1232 Trimetazidine-mediated cardioprotection during ischaemia is mediated by mitochondrial respiratory chain's complex I activity

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Trimetazidine (TMZ) was reported to protect myocardium from ischemia. However, the mechanisms involved in this protection remain a matter of debate. To better understand this topic, we developed an animal model of global myocardial ischemia, using a Lagendorff perfusion system. Thirty Wistar rat hearts were distributed in 3 experimental groups - A - 180 minutes of perfusion with a modified Krebs solution, B - 60 minutes of perfusion with the same solution, followed by 120 minutes of ischemia, in the absence of glucose and O2 and C - as in B, but in the presence of TMZ 25 μM. Mitochondria were then isolated and used to determine the activity of complexes I, II-III and IV of the mitochondrial respiratory chain (MRC), using their metabolic substrates (Glutamate/Malate, Succinate and Ascorbate/TMPD). Parameters evaluated were: Respiratory Control Ratio (RCR), Maximum Mitochondrial Membrane's Electrical Potential (Delta Psi), Phosphorylative Lag Phase (PLP) and Enzymatic Activities (EA) of MRC's complexes.
TMZ significantly improved RCR values, near to those of controls. A significant improvement of Delta Psi values in all the MRC complexes studied was also seen after TMZ treatment, without any significant change in PLP. TMZ significantly improved the enzymatic activity of MRC's complex I, even above the values of group A (control); in the other enzymatic complexes, the impact of TMZ was reduced or none.
Results:

Parameters/groups	Ischemic (Group B)	TMZ (Group C)
RCR	56±5%	101±16% *
Delta Psi (Glutamate/Malate)	89±2%	95±1% *
EA (Complex I)	63±5%	154±11% *
EA (Complexes II-III)	60±5%	66±4%
EA (Complex IV)	71±7%	71±5%

Note: * - p<0.05 B vs C; values are expressed as % of control (Group A).

In conclusion, TMZ improved the efficiency of the oxidative system, with a better preservation of the electrochemical gradient within the inner mitochondrial membrane, without changing the phosphorylation. These mechanisms, involved in the cardioprotective effect of TMZ, are dependent on an increase in Complex I activity.

GENE DELIVERY TO CARDIAC TISSUES

P1233 Enhancement of in vitro gene transfer to smooth muscle cells by ultrasound

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Background: Gene therapy is a promising technique to prevent restenosis following percutanous coronary intervention and increase transfection efficiency is a major step before clinical applications. Ultrasounds (US) combined with agent contrast (gas bubbles) enhance mammalian cells membrane permeabilization and could increase gene transfer in smooth muscle cells (SMC). We evaluated the potential of this method to improve in vitro transfection in SMC.
Methods: SMC were obtained by outgrowth from explants of rabit thoracic aorta and cultured in DMEM containing 20% fetal veal serum. At one month growth cultured SMC were suspended in cell wells (1.10 6 cells per well) in presence of plasmid (pEGFP-N1) and exposed to US. US were performed with a 10 cm^2 surface, 1.656 MHz, piezoelectric ceramic transducer placed below cell wells on continuous mode. Transfection efficiency was optimized by varying US conditions (20 to 50 W; 30 to 60 s exposure time), plasmid concentrations (2,5 μg/ml and 5 μg/ml), adjunction of contrast agent (200 mg μparticles/ml). Cell counts, viability (uptake of 7 AAD) and transfection (GFP fluoscein) were assayed by flow cytometry.
Results: Below 50 W and 50 s US exposure, we did not observed an increase of SMC death. Optimal protein production following 30 W, 40 s exposure was no different in tested DNA concentration (2.5 μg/ml vs 5 μg/ml; p ns). Maximal gene transfection was seen with adjunction of contrast agent (1,53% with contrast agent vs 0,5% without contrast agent) without increasing mortality (8.5% vs 7.5%, p ns). US enhance significantly SMC transfection efficiency (1.53% naked DNA with US versus 0.06% with naked DNA alone; p=0.046) with 2,5 μg/ml of DNA, 100 μl/ml of contrast agent, 30 W and 40 s of US exposure. No increase of cell death was observed.
Conclusions: Ultrasounds combined with contrast agent enhance gene transfer and appears to be a safe technique to be developped for in vivo applications.

P1234 Recombinant Semliki Forest virus: perspectives for selective gene delivery in vascular lesions during stenting

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Background: Previously, we demonstrated that recombinant Semliki Forest virus (SFV) is a more selective vector to cultured vascular smooth muscle cells (VSMC) than Adenovirus (Ad5). Here we describe the consequences for in vivo vascular gene delivery after vector administration through dwelling or a stent.
Methods: SFVLacZ or Ad5LacZ was administered through intraluminal dwelling into balloon-injured rat abdominal aorta. After 3 to 72 h the aortic segments were screened for LacZ staining. In separate experiments, especially designed coverstents (Medtronic, Maastricht, the Netherlands) were used to deliver SFVLacZ or Ad5LacZ (1e8 infectious units/stent). After 48 h and 72 h resp. LacZ expression was studied.
Results: Both SFV and Ad5 expression started after 12 h. However, SFV was more selective than Ad5 with respect to gene transfer in the media (table 1). Both vectors were successfully delivered with coverstents. However, in contrast to dwelling delivery, stent delivery led to LacZ expression to appear almost exclusively in the media.
Discussion: SFV and Ad5 have very distinct gene delivery patterns in balloon-injured vessels after dwelling delivery. However, in-stent delivery of SFV and Ad5 is feasible and leads to transgene expression to be present almost exclusively in the media.

Table 1: in vivo gene delivery

vector type	time [hrs]	positive sections [% of total # of sections]	distribution intima	media	adventitia
SFVLacZ	12	4 (2)	0	0	100
	24	31 (8)	0	90	23
	48	12 (5)	0	33	67
	72	3 (2)	0	0	100
Ad5LacZ	12	23 (8)	32	0	68
	24	8 (4)	0	0	100
	48	29 (14)	0	0	100
	72	27 (4)	18	24	100

SFV and Ad5 transfection into balloon-injured rat aorta. Per aortic segment 5e7 infectious virus units were delivered intraluminally to dwell for 10 minutes. LacZ expression was studied at the given time points. The gene delivery distribution per vessel layer is expressed as % of the total number of LacZ-positive sections. Standard errors are mentioned between brackets.

P1235 Lentivirus (HIV) vector system for gene delivery into cardiac myocytes

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Human immunodeficiency virus (HIV, lentivirus) type-1 vector has a number of attractive features for gene therapy, including the ability to transduce non-dividing cells and long term transgene expression. We used a three plasmid expression system to generate pseudotyped lentivirus vector to investigate the transduction efficiency in the cardiac myocytes (CM). Both lentivirus vector and murine retrovirus vector effectively transduced into dividing cardiac fibroblasts at the same efficiency. Lentivirus vector also efficiently transduced into CM and yielded titers of 4.9x10(5) transducing units/ml (TU/ml), however murine retrovirus vector showed low transduction efficiency with titers reaching only 8.9x10(2) TU/ml. SIN (self inactivating) lentivirus vector known to be third generation lentivirus vector (a portion of 3'-LTR is deleted for reducing promoter interference) has reported to show higher levels of transgene expression than that of full length 3'-LTR lentivirus vector (1st generation of lentivirus vector). Next we investigated the transgene expression levels in CM transduced by 1st generation of lentivirus vector or SIN lentivirus vector. SIN lentivirus vector showed higher transduction efficiency into CM than that by 1st generation of lentivirus vector (6.7x10(5) vs 4.9x10(5)). Furthermore, GFP expression level (mean fluorescence) was higher in CM transduced by lentivirus vector than 1st generation of lentivirus vector (4.2x10(3) vs 1.8x10(3)). These results firstly demonstrated that lentivirus vector can efficiently transduce well-differentiated CM. This appears to be an efficient method and provide a new tool for research and therapy for cardiovascular diseases. μ

P1236 Catheter-based adenoviral overexpression of tissue factor pathway inhibitor reduces intimal hyperplasia in a rabbit injury model

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Background: Tissue factor (TF), the major procoagulant of the atheroma and activated blood monocytes, is locally expressed at the site of balloon injury mediating a prolonged prothrombotic state. TF-pathway inhibitor (TFPI) regulates hemostasis as well as mitogenic and chemotactic effects of coagulation factors VIIa, Xa and thrombin.
Aim: To interfere with the process of restenosis by percutaneous overexpression of TFPI.
Method and Results: Myc-tagged TFPI (Ad5-TFPI-c-myc; n=10) or control virus (Ad5 lacZ, n=10) adenoviral transfection (1x109 pfu/ml) was performed in femoral arteries of atherosclerotic NZW rabbits using a drug delivery catheter. Arterial expression of the transgene was confirmed by immunohistochemistry on day 2, 5 and 21 after percutaneous overexpression in media and neointima smooth muscle cells. Restenosis as quantitated by intima to media (I/M) ratio was significantly reduced 21 days after angioplasty by 63% in Ad5-TFPI-c-myc treated arteries (0.9±0.4) compared with Ad5-lacZ (2.7±0.7) treatment ($p<0.0001$) resulting in 30% luminal gain. Reduced monocyte infiltration and vascular TF expression was observed in Ad5-TFPI-c-myc transfected vessels compared with control
Conclusion: Catheter-based adenoviral overexpression of TFPI reduces intimal hyperplasia in response to balloon injury by inhibition of TF and recruitment of monocytes in the atherosclerotic rabbit injury model.

P1237 High-level and long-term gene expression in endothelial cells transduced by lentiviral vector

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Endothelial cells (EC) are an attractive target for gene therapy. Lentivirus vector is known to infect with wide variety of cells and shows the long term transgene expression. In this study, bovine aortic endothelial cells (BAEC) were infected in vitro with lentivirus vector compared with retrovirus and adenovirus. Transduction efficiency (TE) of b-Gal gene transfer in BAEC by adenovirus, lentivirus, or retrovirus at MOI 10 (Multiplicity of infection) (determined on HeLa cells) is 69, 33, or 22% respectively. In adenovirus and lentivirus, almost 100% of BAEC were transduced at MOI 50. However, in retrovirus, TE showed only 48% at MOI 50 and no increase at MOI 100. The percentage of b-Gal positive cells was decreased rapidly at longer passage of cells after transduced by adenovirus. However, lentivirus and retrovirus showed sustained higher percentage of positive cells. SIN lentivirus vector (a portion of 3-LTR is deleted for reducing promoter interference) showed higher levels of transgene expression than that of full length 3-LTR lentivirus vector at the same MOI. Lentivirus vector showed high TE and long term expression in BAEC. Our results suggest that lentivirus can be an effective vector for the ex vivo genetically modified EC implantation and in vivo gene therapy.μ

P1238 Gene delivery method and immune status determination – Efficacy and safety of adenoviral cardiovascular gene transfer

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Background: Adenoviruses are favored gene transfer vectors in cardiovascular applications. However, the effect of pre-existing immunity on the efficacy of different adenoviral cardiac gene transfer methods is unknown. Methods: The effect of immune status on transgene expression levels was compared following regional retrograde myocardial gene transfer and after local coronary intramural gene transfer. Adenoviral vectors expressing luciferase (5x10(10) pfu) were injected retrogradely in the cardiac vein using an occlusive balloon catheter, and locally in the LAD vessel wall using the Infiltrator catheter in naive pigs (n=12) and in pigs immunized by prior IV injection of the adenoviral vector (n=11). Neutralizing antibody (NAb) titers were assessed by the serum concentrations reducing adenovirus infectivity by 50% of control values in an in vitro infectivity assay. Titers were compared to pre-existing NAb titers in 26 patients referred for CABG. Results: Immunization with adenovirus elicited high NAb titers (1:2000) in all pigs. Myocardial luciferase expression levels [median, 25 and 75 percentiles (25p, 75p), light units, LU/mg protein], following regional gene transfer were abrogated in the left ventricular anterior wall in immunized versus naive pigs (1.26x10(3); 25p: 3.2x10(2), 75p: 5.2x10(3) vs 2.6x10(6); 25p: 9.2x10(5), 75p: 3.2x10(6) LU/mg protein, $P<0.01$). Following intramural gene transfer, however no difference in intramural transgene expression levels (1.46x10(5); 25p: 4.69x10(3), 75p: 3.1x10(5) vs 1.09x10(4); 25p: 2.57x10(3), 75p: 5.79x10(4) LU/mg protein, P=NS), nor in vascular adenoviral mRNA (0.34; 25p: 0.09, 75p: 1.9 vs 0.3; 25p: 0.03, 75p: 4.1 fg viral RNA/ ng GAPDH RNA, P=NS) was observed in immunized versus naive pigs. Transgene expression in the heart following regional gene transfer was associated with a grade I mild interstitial infiltrate (SHLT Cardiac Rejection Score) in all naive pigs, but a grade III-IV moderate to severe inflammation with myocyte necrosis and apoptosis was detected in immunized animals. In CABG patients high titer of pre-existing NAb (>1:2000) was detected in 10/26 patients. Conclusions: Pre-existing anti-adenoviral immunity abrogates cardiac transgene expression. Reduction in transgene expression levels with significant local toxicity was detected in immunized pigs following regional, but not after intramural gene transfer, and mandates screening for pre-existing anti-adenovirus immunity in patients prior to regional myocardial adenovirus gene delivery. Intramural adenoviral gene transfer, in contrast, may obviate these restrictions.

NEW INSIGHTS IN DILATIVE CARDIOMYOPATHY

P1239 Growth hormone administration as immunomodulatory treatment in patients with idiopathic dilated cardiomyopathy: a randomized crossover study

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Background: Recent studies have shown that an abnormal proinflammatory cytokine expression and apoptotic process contribute to adverse left ventricular remodeling and progress of chronic heart failure (CHF). The present study investigates the effects of growth hormone (GH) administration on serum levels of representative proinflammatory cytokines, anti-inflammatory cytokines and soluble apoptosis mediators in patients with chronic heart failure secondary to idiopathic dilated cardiomyopathy (ICD).
Methods: Serum levels of proinflammatory cytokines tumor necrosis factor-a (TNF-a), soluble TNF receptors (sTNFRI, sTNFRII), interleukin-6 (IL-6)and soluble IL-6 receptor (sIL-6R),anti-inflammatory cytokines interleukin-10 (IL-10)and transforming growth factor-b2 (TGF-b2), and soluble apoptosis mediators soluble Fas (sFas) and soluble Fas Ligand (sFasL) were determined (ELISA method) in 10 patients with IDC (NYHA class III; EF 24±2%) before and after a 3-month subcutaneous administration of GH 4IU every other day (randomized crossover design). Peak oxygen consumption (VO2max) was also used to evaluate the functional status of IDC patients.
Results: Treatment with GH produced a significant reduction in serum levels of TNF-a (8.2±1.2 vs 5.7±1.1 pg/ml, $p<0.05$), sTNFRI (3.9±0.4 vs 3.2±0.3 ng/ml, $p<0.05$), sTNFRII (2.6±0.3 vs 2.2±0.2 ng/ml, $p<0.05$), IL-6 (5.5±0.6 vs 4.4±0.4 pg/ml, $p=0.05$), sIL-6R (32.7±3.0 vs 28.2±3.0 ng/ml, $p<0.05$), sFas (4.4±0.8 vs 3.1±0.6 ng/ml, $p<0.05$), and sFasL (34.2±11.7 vs 18.8±7.3 pg/ml, $p<0.01$)in IDC patients.No significant differences were observed in anti-inflammatory cytokines IL-10 (12.1±1.3 vs 13.6±1.7 pg/ml, p:NS) and TGF-b2 (18.8±2.2 vs 18.2±1.6 pg/ml, p:NS) after the GH treatment.However, a significant increase in ratio IL-10/TNF-a (1.8±0.3 vs 3.6±1.0, $p<0.05$) was found with GH treatment. A significant improvement was also observed in VO2max after the completion of 3 months' treatment with GH (15.0±0.8 vs 17.2±1.0 ml/kg/min, $p<0.05$). Good correlations were found between GH-induced increase in ratio IL-10/TNF-a and increase in VO2max ($r=0.76$, $p<0.01$), as well as between GH-induced reduction in sFasL and increase in VO2max ($r=-0.56$, $p=0.08$).
Conclusions: GH administration modulates beneficially circulating cytokine network and soluble Fas/FasL system in patents with IDC. These anti-inflammatory and anti-apoptotic effects may be associated with the improvement in clinical performance and exercise capacity of IDC patients.

P1240 Cardiodepressant effect on cardiomyocytes predicts acute and prolonged haemodynamic benefit during immunoadsorption

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Background: Immunoadsorption (IA) represents an additional therapeutic approach in patients suffering from dilated cardiomyopathy (DCM). The present study characterizes in isolated cardiomyocytes the inotropic effects of serum antibodies in DCM patients (n = 31, EF < 30%) before IA therapy. We compared these inotropic effects in cardiomyocytes with the hemodynamic benefit of the DCM patients during IA.
Methods: Before IA from 31 DCM patients the serum antibodies were purified by anti-IgG separose and dialyzed (100 KD) against experimental buffer. We analysed the effects of the purified antibodies (300mg/L) on cell contraction (video edge detection) and on calcium-dependent fluorescence using fura-2-AM in isolated field-stimulated adult rat cardiomyocytes. Cardiodepressant effects were defined by a reduction of the calcium transient (>5%) and a simultaneous reduction of systolic cell shortening (>10%). After this in-vitro analysis, in all patients IA was performed in 4 courses, at one-month intervals until month three.
Results: Serum antibodies from 21 patients (cardiodepressant group) induced a reduction of calcium transient (-27.2 ± 2.3%) and cell shortening (-34.2 ± 2.2%) ($p<0.001$) on cardiomyocytes. In contrast, antibodies from 10 patients (non-cardiodepressant group) did not influence calcium transient or cell shortening. During the first IA course patients of the cardiodepressant group showed an acute increase in cardiac index from 2.1 ± 0.2 to 2.9 ± 0.1 l/min/m^2 ($p < 0.001$). In contrast, in the non-cardiodepressant group hemodynamics did not significantly change throughout the three months of IA therapy. The prolonged effects were also different in both groups. The cardiac index before the last IA course was 2.1 ± 0.2 l/min/m^2 in the non-cardiodepressant group and 2.9 ± 0.1 l/min/m^2 in the cardiodepressant group ($p < 0.001$). In addition, during IA therapy after three months left ventricular ejection fraction increased in the non-cardiodepressant group from 23 ± 2 to 24 ± 3% (n.s.) and in the cardiodepressant group from 23 ± 2 to 30 ± 2% ($p < 0.01$). Additional in-vitro analysis showed that the cardiodepressant effects are mediated by antibodies of the IgG-3 subclass.
Conclusions: Cardiac antibodies may play a functional role in DCM. Evidence for cardiodepressant antibodies predicts the acute and prolonged hemodynamic benefit induced by IA. The antibodies which induce the inotropic effects belonging to IgG-3.

P1241 The results of long-term idebenone therapy for myocardial involvement in Friedreich's ataxia: a strain and strain rate imaging study

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Background: In Friedreich's Ataxia (FA) there is no standard treatment currently available for the related myocardial disorder despite causative gene and protein identification. However, 2 preliminary studies on Idebenone therapy, a coenzyme Q10 analogue and free-radical scavenger which potentially could reverse the myocardial abnormalities, have shown conflicting results on left ventricular mass regression in FA.
Study Aims: To investigate the effect of long-term Idebenone administration in FA patients with cardiac hypertrophy on a) left ventricular mass index (LVMI) (g/m^2) and b) regional myocardial function. These were evaluated by 1) standard echocardiography, 2) myocardial velocity profiles (VEL) (cm/sec) and 3) peak systolic Strain Rate (SR) (unit S^{-1}) and peak systolic Strain (S) (%).
Methods: 7 FA patients with hypertrophic cardiomyopathy (age 8.5-27 yrs) were studied at baseline (Pre) and after 12 months Idebenone (360mg/d) therapy (12M).
Results: Post-therapy there was a marked improvement in ejection fraction (%) (Pre:77±10, 12M:86±4,p=0.02) and a reduction in LVMI (Pre:126±29,12M: 101±26,p=0.03). Only 1 patient had no mesurable reduction in LVMI. In the 6 remaining patients, there were significant improvements in ultrasound-based deformitation indices in all left ventricular walls studied (septum: basal segment SR: (Pre) -0.9±0.3 vs -1.5±0.5, p=0.04; middle segment SR: (Pre)-1.1±0.3 vs -1.6±0.4, p=0.027; middle segment S: (Pre)-17±6 vs -23±8, p=0.027; average SR: (pre)-1± 0.2 vs -1.6±0.5, p= 0.04; average S: (Pre) -14±5 vs -22±9, p=0.04. Lateral wall: middle segment SR: (Pre)-0.8±0.6 vs -1.6±0.7, p=0.04; average SR: (pre)-1.0±0.3 vs -1.7±0.6, p=0.04. Posterior wall SR: (pre) 1.9±0.5 vs AT = 3.0±0.6, p=0.027).
Even in the patient with no detectable reduction in LVMI (M-mode echo) we could measure an increase in peak systolic SR in the lateral wall (from -0.2 to -0.88 unit S^{-1}), suggesting an early change in regional contractility, not detectable by M-mode echo. Interestingly, there was no change in regional peak systolic myocardial velocities in any of the 7 patients.
Conclusion: In our study, long-term Idebenone therapy significantly improved LVMI, ejection fraction and regional myocardial contractility as assessed by peak systolic SR. Moreover, SR was able to detect even subtle changes in patients where there was no LVMI reduction on standard gray scale imaging. Our findings would suggest that SR and S imaging, but not VEL, should be routinely used in the follow-up of these patients to evaluate improvement in regional myocardial function.

P1242 Interventricular and intraventricular asynchrony: contribution to functionnal and haemodynamic status in dilated cardiomyopathy

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Left and right intraventricular asynchrony and interventricular asynchrony may all contribute to the alteration of the functionnal and the hemodynamic status in heart failure but few informations are available about the separate contribution of each dysynchrony in this degradation.
Methods: A total of 103 patients (pts) with idiopathic dilated cardiomyopathy (IDC) (WHO criteria; normal coronary angiography in all pts; mean age 51 years; range 18-70; 89 men; left ventricular ejection fraction 27 ± 11%) were studied. Left bundle branch block was present in 25% of the pts and mean QRS duration was 113 ± 32 ms. Equilibrium radionuclide angiography with Tc99m was performed and Fourier phase analysis were examined in both ventricles. Interventricular delay between the mean phase of RV and LV assessed interventricular asynchrony and standard deviations (SD) of the mean phase in each ventricle assessed intraventricular asynchrony.
Results: Among patients with LBBB, interventricular delay was more marked (51±66 vs 16± 35 ms, p=0.001) as was left intraventricular asynchrony (SD of LV mean phase 77±41 vs 50±22 ms, $p<0.0001$). Increase in SD of RV phase was related to a higher NYHA class (R=0.22, p=0.02) and a lower peak oxygen uptake(R=-0.44, p=0.0001). LV end diastolic diameter was highly correlated with SD of LV phase (R=0.59, $p<0.0001$) and to SD of RV phase (R=0.38, p=0.0001) but poorly with IV delay (R=0.2, p=0.04). LV ejection fraction did not correlate with IV delay but was inversely related to SD of LV phase (R=-0.52, $p<0.0001$) and to SD of RV phase (R=-0.41, $p<0.0001$). Cardiac index was inversely related to SD of LV and RV phase (R=-0.23, p=0.03 and R=-0.30, p=0.006) and did not correlate with IV delay. With a follow-up of 27 ± 23 months, 18 patients had a major cardiac event (7 cardiac deaths, 11 worsening of heart failure leading to heart transplantation). SD of the LV and RV mean phase were predictors of cardiac event (all $p<0.0001$) but interventricular delay was not (p=0.35).
Conclusion: The prognosis of congestive heart failure seems related to left and right intraventricular rather than to interventricular asynchrony in IDC. Moreover, all the parameters of functionnal and hemodynamic status are much better related to left and right intraventricular dysynchrony than to interventricular asynchrony.

P1243 Meta-analysis of 267 subjects with lamin mutations: are conduction disorders reliable indicators of lamin mutations?

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Purpose: Mutations in the gene for nuclear lamin A/C can cause familial dilated cardiomyopathy (DCM), skeletal myopathy (SM) or both. Our purpose was to relate the clinical phenotype to the various known mutations.
Methods: We conducted a meta-analysis of all published patients described with a mutation in lamin A/C responsible for familial DCM and/or skeletal myopathy. Patient characteristics and localisation of gene mutation were analyzed.
Results: In total 267 patients with a lamin A/C mutation have been described. 106 pts (40%) demonstrated isolated DCM without SM. 150 pts (56%) demonstrated evidence of conduction system disease (CSD) or supraventricular arrhythmias before onset of DCM, 77 pts (29%) required a pacemaker. 95 pts (36%) demonstrated SM with arrhythmias or CSD and only a minority demonstrated isolated SM. 24 pts (9%) with isolated DCM died suddenly whereas 11 pts (4%) with SM died suddenly. No de novo mutations have been described for DCM or LGMD. Mutations occurred at various positions of the lamin gene, without clear relation to the clinical phenotype.
Conclusion: This meta-analysis is the first to provide additional insights into the clinical cardiological manifestations of lamin mutations:
1. conduction system disease invariably precedes DCM
2. 25% of patients with isolated lamin-DCM die suddenly.
Therefore, lamin A/C cardiomyopathy can be recognized in advance of clinical DCM by the combination of CSD and a positive family history.

P1244 Clonal T-cell composition, detected by family specific PCR of the T-cell receptor beta chain, is exclusively present in dilated cardiomyopathy

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Background: Autoimmunity, resulting from molecular mimicry between viral and cryptic cardiac antigens, is postulated for the pathogenesis of dilated cardiomyopathy (DCM). Autoimmunity directed against distinct antigens evokes expansion of specific T-cell clones infiltrating the target tissue. This phenomenon leads to a clonal predominance of T-cells harboring an identical rearranged T-cell receptor gene (TCR), which can be reliably identified by family specific PCR for the Vb-N-Db-N-Jb-region of the TCR gene in combination with the GeneScan-analysis (Assaf et al., Blood 2000).
Materials and Methods: DNA extracted from explanted DCM hearts (n=17, 1 female; 49±13 years; LVEF: 18±5%) were investigated for clonality of the TCR-b-gene. Non-DCM-hearts (ischaemic cardiomyopathy: n=2, valvular heart disease: n=3, donor hearts: n=3) served as controls. The TCR-b PCR-products analyzed by high-resolution fragment analysis (GeneScan), displayed a Gaussian-like distribution profiles in polyclonal and single dominant peaks in clonal T-cell populations. Clonal TCR-b PCR-products were directly sequenced.
Results: The GeneScan analysis of the TCR-b PCR-products demonstrated a clonal T-cell population in n=9/17 (53%) of the DCM hearts. In contrast, exclusively polyclonal composition of the TCR-b PCR-products were obtained from the non-DCM hearts. Sequence analysis of the clonal TCR-b PCR-products from the n=9 DCM hearts determined Vb19.01 in n=6 cases (67%), and Vb6-1.01, Vb6-3.01 and Vb10-3.04 in each of the remaining cases.
Conclusions: Clonal T-cell composition is exclusively present in DCM, as detected by PCR and GeneScan analysis of the TCR-b rearrangement. This phenomenon indicates a clonal T-cell proliferation due to specific antigen, which confirms the autoimmune hypothesis of DCM. Our results, demonstrating a clear predominance of Vb19.01 T-cell clones in DCM, warrant the molecular analysis of the respective immunogenic sequence and eventually a TCR-based immunotherapy in DCM (e.g. with DNA vaccines).

P1245 Hematologic correlates of spontaneous echo contrast and echocardiographic parameters in patients with dilated cardiomyopathy

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Objectives: Patients with dilated cardiomyopathy have a high risk for cardioembolic events. However, hematologic characteristics of these patients are not well known. The aim of our study was to investigate the relation of hematologic parameters to spontaneous echo contrast (SEC) and some echocardiographic variables in a group of patients with ischemic dilated cardiomyopathy.
Methods: The study group consisted of 45 patients (32 male, 13 female, mean age 60±11 years) with ischemic dilated cardiomyopathy. All of the study patients were in sinus rhythm and not receiving anticoagulation. Hematologic parameters were measured on the day of transthoracic and transesophageal echocardiographic examination.
Results: Patients with SEC (n=30; 67%) had an increased plasma low-molecular-weight (LMW) heparin (p=0.02), unfractionated (UF) heparin (p=0.01), fibrinogen (p=0.07), lower factor VII (p=0.09) and left atrial appendix emptying velocity (p=0.01). Multivariate analysis showed that SEC was independently related to left atrial appendix emptying velocity (p=0.004), fibrinogen (p=0.05) but not to other hematologic parameters.
Left atrial and right ventricular diameter had a significantly positive correlation to activated partial thromboplastin time (r=0.36, p=0.03 and r=0.41, p=0.01 respectively). Another positive correlation was observed between left ventricular systolic function and factor VII (EF: r=0.38, p=0.04; FS: r=0.38, p=0.04). Patients with restrictive diastolic filling had significantly higher LMW and UF heparin (p=0.03 and p=0.03). Grade of mitral regurgitation had no correlation to any hematologic parameters. Left atrial appendix emptying velocity showed a positive correlation with FVII (r=0.42, p=0.007) and a weak negative correlation with LMWH and UFH.
Conclusion: Patients with dilated cardiomyopathy and left atrial SEC have a tendency for increased coagulation and also for probable compansatory anticoagulation. The paradoxical decrease of FVII and increase of LMW and UF heparin in patients with worse left ventricular and atrial appendix function suggested an increased tendency for spontaneous intrinsic anticoagulation in patients with dilated cardiomyopathy and severely impaired left ventricular systolic and diastolic function.

P1246 From acute myocarditis to dilated cardiomyopathy: the role of myocardial catecholamines

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Impact of the adrenergic system activation on hemodynamics in acute myocarditis and dilated cardiomyopathy is controversial.
Methods: In order to elucidate this issue, myocardial catecholamine concentration was assessed in biopsy proven acute myocarditis (BPM)(20 pts, 80% males, mean age 36.5±13.3 years) and idiopathic dilated cardiomyopathy (IDC)(32 pts, 75% males, mean age 47.3±11.9 years). The diagnosis was based on clinical data, echocardiography, cardiac catheterization, and endomyocardial biopsy findings. Myocardial norepinephrine (MNEC), epinephrine (MEC), and dopamine (MDC) concentrations were measured in EMB samples using catechol-O-methyl-transferase radioenzymatic method. The correlation between myocardial catecholamine concentration and left ventricular (LV) hemodynamics was also calculated.
Results: Comparison between the groups revealed significantly higher MNEC and MEC in BPM than in the IDC group (Table). Mean MDC values were similar in both groups (p>0.05). No significant correlation was found among myocardial catecholamine concentration and hemodynamic parameters in BPM pts. In IDC pts, both MNEC and MEC demonstrated significant positive correlation with LVdp/dt max and LVEF, and significant negative correlation with pulmonary capillary pressure and LVEDP.
Conclusions: significantly higher MNEC and MEC were found in BPM than in IDC group. Depressed LV function, decreased MNEC and MEC concentrations, as well as their good correlation in IDC group, may reflect myocardial dysfunction and indicate final stage of the disease.

Abstract P1246 – Table

Invasive hemo-dynamics	MNEC-BMP 415.4±71.1 ng/g	MNEC-IDC 262.2±68.9 ng/g¶	MEC-BMP 57.3±4.8ng/g	MEC-IDC 35.8±6.2 ng/g¶¶	MDC-BMP 76.6±9.2 ng/g	MDC-IDC MDC-IDC 70.1±11.8ng/g
HR (b/min)	-0.29	0.35	-0.16	0.49	-0.27	0.09
PCWP mean (mmHg)	-0.22	-0.83*	0.17	-0.76**	-0.16	-0.07
LVEDP (mmHg)	-0.09	-0.79**	-0.13	-0.75**	-0.23	-0.11
LV dp/dt max (mmHg/s)	0.33	0.87**	-0.18	0.74**	-0.09	0.07
LVEF (%)	0.34	0.89**	0.08	0.86**	-0.02	0.02
MAP (mmHg)	0.12	-0.01	0.26	0.17	0.01	-0.08

The correlation of myocardial norepinephrine (MNEC), myocardial epinephrine (MEC), and myocardial dopamine (MDC) concentration and hemodynamic variables in biopsy proven myocarditis (BPM) and idiopathic dilated cardiomyopathy (IDC), *-p<0.05, **-p<0.01; ¶ - MNEC in BMP vs. IDC (p<0.01), ¶¶ - MEC in BMP vs. IDC (p<0.01)

P1247 Induction of activating antibodies against human β1-adrenoceptors results in progressive left ventricular dilatation and dysfunction in rats

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Purpose: A subgroup of patients with dilated cardiomyopathy (DCM) has been shown to have functionally active antibodies (Ab) against the second extracellular domain of the beta1-adrenergic receptor (b1-ECII). To investigate whether antibodies against b1-ECII (100% sequence-identity human/rat) might be involved in the pathogenesis of DCM we attempted to generate immune-cardiomyopathy in the rat.
Methods: N=35 Lewis-rats were were immunized monthly over 15 months either with fusion proteins of glutathion-S-transferase (GST) and the human b1-ECII (n=15), with GST alone (n=10), or with 0.9% NaCl (n=10). Rat-sera were screened for anti-b1-ECII Ab by ELISA, Western blotting, and immunofluorescence using Sf9- and CHW-cells expressing recombinant human b1-adrenergic receptors. In parallel, echocardiography was performed every three months (GS Vingmed, System FiVe) followed by left heart catheterization (Millar-tip-catheter) and subsequent excision of the hearts at month 15.
Results: High titers of anti-b1-ECII Ab were found throughout the study-period in all 15 immunized rats, but not in control rats. Anti-b1-ECII recognized denatured (Western blot) as well as native b1-receptors (immunofluorescence) and increased both basal and stimulated cAMP-levels in stably transfected b1-CHW-cells (functional assay). Compared with controls [C], echocardiographic follow-up revealed significant left ventricular dilatation and dysfunction in anti-b1-ECII-positive rats [b1] from the ninth month on, which progressed during the study (LVED: 8.2±0.1 [b1] vs. 7.1±0.3 mm [C]; FS: 33.7±2.9 [b1] vs. 41.1±1.1% [C]; $p<0.01$). The data obtained by cardiac catheterization (i.e. contractility dP/dt: 8113±208 [b1] vs. 10050±289 mmHg/s [C]; $p<0.001$) and the relative heart-mass (2.75±0.05 [b1] vs. 2.50±0.03 mg/g [C]; $p<0.001$) confirmed the echocardiographic results.
Conclusion: Our study shows that rats immunized against the b1-ECII-domain develop activating anti-b1-receptor antibodies and, subsequently, progressive left ventricular dilatation and dysfunction. However, to establish autoimmunity as a pathogenic principle it will be necessary to demonstrate that immune-cardiomyopathy may be induced also by transferring anti-b1-ECII to healthy animals.

P1248 LMNA defects and nuclear membrane damage in autosomal dominant dilated cardiomyopathy with atrio-ventricular block

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Familial dilated cardiomyopathy (DCM) associated with either conduction disturbances or variable myopathy has been reported to be causally linked to lamin A/C gene (LMNA) defects. LMNA gene, myocardial ultrastructural changes and protein expression were analysed in familial and sporadic DCM associated with either atrioventricular block (AVB)(n=16; 8 familial and 8 sporadic) or increased serum creatin-phosphokinase (sCPK)(n=9). Six novel LMNA mutations were identified in the 6 autosomal dominant forms with AVB (R89L, K97E, E111X, R190W, E317K, four base pair insertion at 1713 cDNA)(6/16: 37%). The immunostain with anti-lamin A/C antibodies showed reduced or absent expression of the protein in the myocyte nuclei, while endothelial and interstitial mesenchimal cells retained normal immunostain. In 3 hearts with different mutations the Western blot showed an additional 30 kDa band, suggesting degrading effect of the mutated on the wild type protein. The atrioventricular junctions of the 3 hearts excised at transplantation showed fibro-fatty changes and myocyte degeneration. Focal disruptions, bleb formation and nuclear pore clustering were documented at electron microscopy in the myocyte nuclear membranes. None of the above changes were found in controls, both disease and normal cases. The LMNA gene mutations account for 37% of the DCMs with AVB, all familial autosomal dominant. In these patients, we demonstrated decreased expression of lamin A/C, protein degradation, structural damage of the myocyte nuclear membrane, and degenerative changes of the atrioventricular junction.

P1249 Familial non-X-linked dilated cardiomyopathy: progression to the disease in asymptomatic "healthy" relatives with cardiac abnormalities

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A clinical program dedicated to familial non-X-linked dilated cardiomyopathy (DCM) was lunched in 1995 by our Centre (Eur Heart J 2001; 22:73-81). The program consisted of screening all informed and consenting relatives of patients (pts) consecutively diagnosed with DCM. Since then, we enrolled 130 index pts and 557 family members. Familial DCM was diagnosed on evidence-based data with at least two members proven as affected. Of the 557 relatives, 61 were excluded at time 0 (T0) and 3 at time 1 (T1) because of concomitant relevant disorders (hypertension, diabetes mellitus, coronary artery disease, alcohol consumption, etc.); 273 did not complete the follow-up (FU), while 220 had a 1 to 3-year clinical and instrumental FU (32.1±9.8 months). Of the 220, 18 were found to be affected at T0, leaving a study population of 202 apparently "healthy" subjects. Of the overall 202 healthy relatives, only 2,1 with LVEDD>112% + AVB and 1 with LVEDD>117% + LVFS<25%, developed DCM during the FU. Both were from DCM defined as familial at T0. Of the 20 relatives with >LVEDD, 10 had LVEDD<112% at the FU. LVFS>25% did not predict, by itself, the development of the disease.

Results in 202 healthy relatives

Instrumental Data	Time 0 (#)	Time 1 (#)	FU: from Time O to Time 1
AVB	3	4	3confirmed+1new
Left Anterior Hemiblock	2	3	2confirmed+1new
Left Bundle Brunch Block	0	0	
LVEDD>112%	14	14	3confirmed+11new,7normalized,4worsened
LVEDD>117%	6	9	3confirmed+6new,3normalized
LVFS<25%	2	9	new, 2normalized
LVEF<50%	0	2	1 from LVEDD>112%,1from LVEDD>117%

AVB atrio-ventricular block; LVEDD left ventricular end-diastolic diameter, LVFS left ventricular fractional shortening, LVEF left ventricular ejection fraction

In conclusion, only 2 of 202 healthy relatives (1%) of DCM pts developed the disease during the FU. Instrumental monitoring seems appropriate only in relatives with >LVEDD, either isolated or associated with <LVFS or AVB, especially in proven familial non-X-linked DCM.The rate of disease progression among "healthy" relatives with >LVEDD is low but imposes to continue the FU and the search for new predictive markers, given that the 2 relatives who developed the disease did not differ from the 18 who did not.

P1250 Clinical course of anthracyclines-induced versus idiopathic dilated cardiomyopathy

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Background: About 5% of neoplastic patients (pts) undergoing anthracyclines therapy develop cardiomyopathy. Aim of the study was to analyse the clinical course of pts with anthracyclines-induced cardiomyopathy (AIC), as compared to those with idiopatic dilated cardiomyopathy (IDC).
Methods: Sixty-eight consecutive AIC pts (mean age 51±12 years, sex female 75%) referred to, and investigated at the Cardiology Service of Aviano (careful clinical and non-invasive assessment, including echocardiogram at baseline and at 1-year follow-up), were compared to 136 age- and sex-matched IDC pts enrolled in the Heart Muscle Diseases Registry of Trieste.
Results: AIC pts had been previously treated with adriamycin and/or epirubicin at adriamicyn equivalent-dose (EQD) of 457±152 mg/m^2, for breast cancer (n=41, 60%), lymphoma (n=18, 26%), or other tumours (n=9, 14%); 14 pts (21%) had been also treated with mitoxantrone. Eighteen pts (26%) received mediastinal or left side chest radio-therapy. Pts developed AIC 16±34 months after chemotherapy (CT). At enrollment, in comparison to IDC pts, AIC pts showed higher heart rate (HR 93±20 vs 81±17 bpm, $p<0.0001$), smaller LV end-diastolic diameter (DTD 32±5 vs 38±5 mm/m^2, $p<0.0001$), higher LV ejection fraction (EF 45±6 vs 30±10%, $p<0.0001$), and similar mild symptomatic impairment (NYHA 2.1±0.9 vs 2.0±0.8, p=NS). AIC pts were under-treated in comparison to IDC pts (ACE-inhibitors 71 vs 84%, p=0.027 (EQD enalapril 8.5 vs 21.3 mg, $p<0.0001$); beta-blockers 22 vs 64%, $p<0.0001$ (EQD metoprolol 41 vs 112 mg; $p<0.0001$); diuretics 41 vs 60%, p=0.01; digoxin 54 vs 80%, p=0.0001; anti-arrhythmic drugs 6 vs 31%; $p<0.0001$). At 12-month follow-up, AIC pts showed a less pronounced improvement in LVEF (+4±8 vs +9±11%, p=0.04) than IDC pts, while changes in LVEDD did not differ between the two groups (-1±4 vs -2±5 mm, p=NS). Survival of AIC pts was significantly worse (12, 24, 36 months: 66, 42, 29% vs 96, 94 e 91%, $p<0.0001$), while hospital admissions for cardiovascular reasons tended to be less frequent (12, 24, 36 months: 13, 13 e 13% vs 20, 23 e 27%, p=NS). Thirty-six pts died, 29 of them died for their primary disease (81%) and only 1 for heart failure progression (3%).
Conclusions: As compared to IDC pts, AIC pts are less impaired at enrolment and seem to have a more favourable evolution of cardiomyopathy, in the face of less frequent use/lower dosages of effective heart failure therapies (ACE-inhibitors and beta-blockers). High mortality rates are clearly related to the progression of neoplastic disease.

Day 3

Monday 2 September 2002

ARRHYTHMIAS MECHANISMS

1277 Autoantibodies: new upstream targets of paroxysmal atrial fibrillation in patients with congestive heart failure

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Objectives: We sought to define the clinical implications of autoantibodies (Abs) as upstreams of paroxysmal atrial fibrillation (AF) in patients (pts) with congestive heart failure (CHF).
Methods and Results: Circulating Abs against myosin (M-Abs) detected by immunofluorescence, Abs against beta1-adrenergic receptors (Beta1-Abs) by ELISA, and Abs against Na-K-ATPase (NKA-Abs) by ELISA were screened in 95 CHF pts with left ventricular ejection fractions (LVEF) <45% (coronary artery disease (CAD), n=48; dilated cardiomyopathy (DCM), n=47) and 48 age-matched control pts with hypertension. All pts had no antiarrhythmics and were enrolled with ACE inhibitors at chronic stable states. Relations of the presence of paroxysmal AF to other clinical variables were assessed on 48-hour Holter monitoring. There was no Abs in control pts. However, M-Abs, Beta1-Abs, and NKA-Abs were detected in 22%, 26%, and 16% pts with CHF (CAD; 8, 10, and 4%, DCM; 36, 43, and 28%, respectively). The occurrences of paroxysmal AF were more frequent in DCM than in CAD (47% vs 15%, p<.01). A multivariate analysis suggested that NKA-Abs was an independent risk factor for the occurrence of paroxysmal AF (p<.01), although there were no differences in other clinical profiles; age, gender, NYHA functional class, concomitant medications, LVEF, left atrial diameter, severity of mitral regurgitation, serum potassium, plasma norepinephrine, and atrial natriuretic peptide concentrations.
Conclusions: This study demonstrated that autoantibodies against sarcolemmal Na-K-ATPase were closely related to the occurrence of paroxysmal AF in pts with CHF, and rose the possibility of an autoimmune process as new upstream of AF.

1278 Early atrial ultrastructural remodelling after sustained rapid atrial pacing in a canine model of induced atrial fibrillation

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Recent studies in animal models of prolongaded sustained atrial fibrillation described that chronic sustained rapid atrial pacing lead to electrophysiological and atrial structural remodeling. Qualitative and quantitative structural changes of atrial myocardium in the early stages of pacing-induced atrial remodeling are unknown.
Methods: Fifteen halothane-anesthetized adult beagle dogs underwent insertion of a transvenous lead at the right atrial appendage (RAA). Ten dogs were continuously paced at 400 bpm for 3 days and 5 dogs in sinus rhythm served as control. Right atrial effective refractory period (ERP) was measured at either baseline and after 3 days in both groups. After 3 days structural changes of the atrial myocardium were examined and quantified in interatrial septum, lower right atrium (RA), RAA and left atrial appendage (LAA) by conventional and electron-microscopy studies.
Results: Right atrial ERP was significantly shortened after pacing from 136±15 msg to 80±30 msg. In unpaced dogs, atria appeared normal. After 3 days of continuous rapid atrial pacing, electron microscopy of atrial tissue demonstrated ultrastructural changes that were characterized by 1) loss of contractile material 2) changes in mitochondrial size and shape 3) disruption of the sarcoplasmic reticulum and 4) loss of profile of intracellular membranes. Findings correlated with the expression levels of proteins (a-actin, desmin and E-Cadherin) detected by immunohistochemical staining. No evidence of increased connective tissue content and myocyte hypertrophy was documented. Table shows the mean percentage of severely atrial affected myocytes (>25% myolysis) in paced and control dogs.

Quantification of atrial changes

	RAA	Septum	Lower RA	LAA
Paced dogs	11±2%	6±1.5%	8±1.5%	5±1.4%
Control dogs	2±1%	3±1%	2±1%	2±1%
	p<0.001	p<0.001	p<0.001	p<0.01

Conclusions: This is the first study to demonstrate both qualitatively and quantitatively early ultrastructural changes of atrial myocardium in an animal model of pacing-induced atrial remodeling. This finding may have clinical implications for an early approach in patients with atrial fibrillation

1279 A T-type Ca channel blocker efonidipine prevents tachycardia-induced atrial remodelling in dogs

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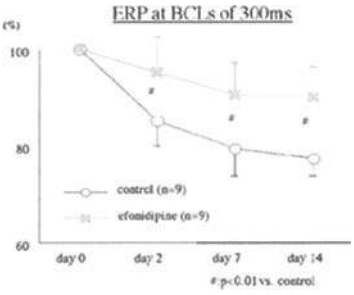
Calcium overload plays a central role in inducing atrial electrical remodeling during atrial tachyarrhythmias. Since the L-type but not T-type Ca^{2+} current is downregulated in this process, a T-type Ca blocker efonidipine may potentially prevent atrial electrical remodeling.
To prove this hypothesis, we measured the atrial effective refractory period(ERP) on the day before, and 2, 7, 14 days after starting atrial pacing at 400 ppm in 9 dogs with chronic oral efonidipine (5mg/kg/day) and in another 9 dogs without drug (control). In response to rapid pacing, ERP decreased progressively in the control dogs, whereas in the efonidipine group, ERP did not change significantly and remained greater than that in the control dogs.



ERP at 300 bpm.

In conclusion, efonidipine, a T-type Ca blocker, is highly effective in preventing atrial electrical remodeling.

1280 Load mismatch at tissue discontinuities underlies progressive ventricular activation delay at long cycle lenghts

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Progressive ventricular activation delay (PAD) starting at long coupling intervals of premature stimulation has been shown to correlate with sudden cardiac death in patients with and without heart disease. The underlying mechanism of PAD is still unknown. Studies carried out in explanted human hearts from patients undergoing heart transplantation showed that PAD increased in areas with patchy fibrosis with long strands. The amount of delay depended on the direction of the wave front. We hypothesize that PAD may be caused by the sites of load mismatch imposed by tissue discontinuities due to fibrosis.
Methods: Load mismatch was simulated in cell cultures grown in patterns according to methods developed by Rohr and Kleber. Neonatal rat heart cells were grown in 12 star-shaped structures each with 8 arms (diameter 0.15 mm, length 2 mm). Stimulation was performed at the extremity of one arm only (n=12, group A) and 2 arms (n=6, group B). Extracellular electrograms were recorded at 24 sites, homogeneously distributed over all arms. In group A conduction curves (extrastimulus method) were determined at all recording sites. The mean increase of delay (MID) of the conduction curves was used as a measure of PAD. In group B Wenckebach periodicity (WP) was determined for both pacing sites. The shortest cycle length (CL) of pacing leading to WP was used to pace regularly both arms. Pacing was performed (1) simultaneously; (2) by a phase shift of 10, 20 and 30 ms.
Results: In group A MID was 0.81 ±0.41 ms (per 10 ms) for sites in the paced arm and 3.13 ±0.58 ms in the other arms. PAD started to increase at the transition of the paced arm and the star center. In group B summation of activation at WP-CL resulted to 1:1 conduction without increased delay. Out-of-phase pacing (up to 30 ms) increased activation delay to 31.53 ±6.83 ms. Maximum activation delay during stimulation in one arm was 25.60 ±8.80 ms.
Conclusion: Our data show: (1) Load mismatch causes PAD (2) Summation of activation facilitates conduction but may increase delay.

1281 Propagated conduction heterogeneity of right ventricular outflow tract in evolving canine vagal stimulation

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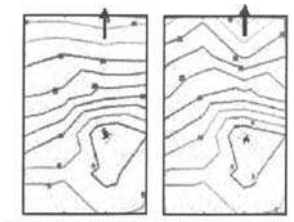
Background: Much attention has been drawn to the role of the autonomic nervous system as a trigger for Brugada and Brugada described idiopathic ventricular fibrillation. The possibility is suggested that the mechanism involved consists of a conduction disturbance existing at right ventricular outflow tract (RVOT) and that this conduction disturbance is aggravated by accelerated vagal activity. The purpose of the present study is to verify the hypothesis that vagal stimulation affects the conduction properties of RVOT.

Methods: In six anesthetized dogs, isochronal mapping at RVOT using multiple electrodes was studied with and without vagal stimulation. The right chest was opened and approximately multiple electrodes were set at RVOT. Two Teflon-coated wire electrodes were embedded in the cardiac end of each vagal nerve.

Results: Without vagal stimulation, conduction properties of RVOT was propagated upward homogeneously from breakthrough point. However, with vagal stimulation conduction properties of RVOT was propagated upward heterogeneously from breakthrough point. Especially with vagal stimulation, conduction properties of RVOT were modulated by every beats.



Isochronal mapping.

Conclusion: This study demonstrates that propagated conduction heterogeneity of right ventricular outflow tract was evolved by vagal stimulation. We propose that the mechanism involved consists of a conduction disturbance existing at the RVOT is one in which the propagated conduction heterogeneity is mainly located from the anterior wall to the RVOT but may also be modulated by every beats. Propagated conduction heterogeneity of right ventricular outflow tract by accelerated vagal activity may be important in arrhythmogenesis for Brugada and Brugada described idiopathic ventricular fibrillation.

1282 Cardiac autonomic dysfunction in patients with non-ischaemic ventricular tachyarrhythmias

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In patients with nonischaemic ventricular tachyarrhythmias (VT/VF), the potential role of the cardiac autonomic nervous system in arrhythmogenesis is indicated by the predominance of VT/VF occurrence during either adrenergic or vagal stimulation. In arrhythmogenic right ventricular cardiomyopathy (ARVC) and idiopathic right ventricular outflow tract tachycardia (RVO-VT), VT/VF are frequently provocable by exercise and may be suppressed by antiadrenergic treatment (β-blockers). In contrast, in pts with Brugada syndrome, VT/VF mainly occur at rest or during sleep. In pts with idiopathic ventricular fibrillation (IVF) or long QT syndrome (LQTS), VT/VF may occur during exercise or resting periods.

To assess the presynaptic sympathetic myocardial innervation, 206 pts with nonischaemic VT/VF and 10 control subjects underwent 123I-MIBG SPECT scintigraphy. Quantitative analysis was performed with a 33-segment bull's eye model. 123I-MIBG (analogue to norepinephrine) uptake was defined as abnormal in case of reduction by >2 SD when compared to the same segment in the control group. Abnormal myocardial perfusion was excluded by resting and exercise ECG and coronary angiography in all pts, and by additional Tc-MIBI-SPECT in initial pts.

A regional defect of 123I-MIBG-uptake was present in 136/206 pts (66%) with nonischaemic VT/VF (table). Compared with the control group, the tracer uptake was most frequently reduced in septal and inferior LV areas.

Diseases and MIBG findings

	pts	MIBG abnormal	defect area	sign. vs control
ARVC	n=78	81%	25±14%	P< 0.01
RVO-VT	n=50	62%	25±12%	P< 0.01
IVT	n=28	64%	24±12%	P< 0.05
Brugada	n=20	50%	30±13%	P< 0.05
LQTS	n=30	47%	22±11%	n.s.

Conclusions: Cardiac autonomic dysfunction is frequent in pts with nonischaemic VT/VF as shown by the results of 123I-MIBG SPECT imaging. Autonomic dysfunction may indicate increased adrenergic release and turnover or impaired reuptake of norepinephrine. The imbalance of autonomic myocardial innervation may have significant impact on the arrhythmogenesis in pts with nonischaemic VT/VF.

STROKE IN PATIENTS WITH ATRIAL FIBRILLATION

1288 Mortality and rate of stroke or embolism in atrial fibrillation during long-term follow-up

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Background: Patients with atrial fibrillation have a higher mortality and risk of stroke/embolism than patients with sinus rhythm. Antithrombotic therapy decreases the risk of stroke/embolism but is underused. Aim of the study was to assess the association of clinical and echocardiographic characteristics with mortality and stroke/embolism and the antithrombotic medication in the year 2000.

Methods: Included were 409 outpatients with nonrheumatic atrial fibrillation (62 ± 12 years, 36% female, 39% intermittent atrial fibrillation). Patients with thrombi received anticoagulation, patients without thrombi aspirin until the follow-up in 1995, afterwards anticoagulation according to clinical risk factors was recommended. Primary events were death. Secondary events were stroke/embolism.

Results: Follow-up was 1 to 133 months. The mortality was 4%/year. The cause of death was cardiac (84), fatal stroke (26), malignancy (23), sepsis (5) and unknown (24). Multivariate analysis identified age (risk ratio, 1.06 [CI 1.04 -1.08]; P<0.0001), heart failure (risk ratio, 2.01 [CI 1.31 - 3.0]; P = 0.0013) and good left ventricular systolic function (risk ratio, 0.69 [CI 0.49.- 0.98]; P = 0.0353) as predictors of mortality. The rate for stroke/embolism was 3%/year. Multivariate analysis identified age (risk ratio, 1.05 [CI 1.02 - 1.09]; P = 0.0006) and previous stroke (risk ratio, 2.14 [CI 1.02 - 4.51]; P = 0.0454) as predictors of stroke/embolism. In the year 2000, 51 (21%) of the 247 surviving patients received no antithrombotic medication, 88 (36%) anticoagulants, 102 (41%) aspirin and 6 (2%) low molecular heparin.

Conclusions: Therapy of heart failure and oral anticoagulation in atrial fibrillation should be taken seriously, especially in elderly patients and in those with previous stroke.

1289 Prevalence of atrial thrombi in patients with atrial fibrillation/flutter and subtherapeutic anticoagulation candidates to cardioversion

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In patients with atrial fibrillation/flutter (AF) electrical cardioversion (ECV) is often used to restore sinus rhythm, but the procedure may be associated with clinical thromboembolism. The use of 3 weeks of warfarin before ECV results in a substantial reduction of thromboembolic complications. Nevertheless, in patients scheduled for ECV subtherapeutic INR values are common. An incomplete anticoagulation regimen could expose patients to the risk of post ECV thromboembolism. We retrospectively reviewed all ECV performed by the Cardiology Unit at Ospedale Valduce from June '99 to January 2002. We identified 28 patients with persistent AF in whom a transesophageal echocardiogram (TEE) was performed preliminary to ECV despite prolonged (> 3 weeks) anticoagulation with warfarin. In these patients TEE was done because of subtherapeutic INR values (i.e. < 2) in the 3 weeks preceding the scheduled ECV. A left atrial appendage (LAA) thrombus was identified in 4/28 patients (14%). In patients with LAA thrombus subtherapeutic INR values were lower (1.45±0.09 vs. 1.69±0,2 p=0.003) and LAA emptying velocities on PW Doppler were lower (13.7±4.5 vs. 25.9±12.1 cm/sec, p=0.003) with respect to patients without LLA thrombus. Male gender, presence of structural heart disease, history of hypertension, use of digoxin, presence of spontaneous echocontrast on TEE and arrhythmia type (atrial fibrillation vs. flutter) were not predictors of LAA thrombi. Furthermore, patients with and without LAA thrombi did not show difference in left ventricular (LV) ejection fraction (55.5±16.4 vs. 56.9±7.3% p=NS), LV fractional shortening (35±8.8 vs. 34.4±8.8% p=NS) and left atrial diarneter (42.8±10.4 vs. 41.9±8.4 mm. P=NS).

Concusions: subtherapeutic levels of anticoagulation before elective ECV of AF may expose patients to post-ECV thromboembolic sequelae, especially in patients with lowest INR values. Current recommendations of 3 weeks of therapeutic anticoagulation before ECV of AF > 2 days duration should be firmly observed. In patients with subtherapeutic levels of anticoagulation in the pre-ECV period a TEE-guided ECV might be helpful in reducing thromboembolic complications.

1290 Comparison of transoesophageal echocardiography findings in patients with atrial flutter and atrial fibrillation

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Transesophageal echocardiography (TEE) has been proposed as a method of screening patients (pts) for left atrial thrombus before direct current cardioversion(CV) of atrial fibrillation. Aim of this prospective study was to compare the incidence of left atrial thrombi and spontaneous echo contrast before planned CV in 144 pts with atrial flutter with the incidence in 845 pts with atrial fibrillation and effective anticoagulation (INR 2-3) at least 3 weeks prior to CV.

Methods: TEE studies before planned CV were performed in 144 pts with atrial flutter (77% male, mean age 62 ± 12 years, organic heart disease 56%, hypertension 54%, diabetes mellitus 15%, left atrial diameter 42 ± 6 mm, history of stroke 3.5%) and in 845 pts with atrial fibrillation (72% male, mean age 63 ± 11 years, organic heart disease 60%, atrial hypertension 57%, diabetes mellitus 13%, left atrial diameter 45 ± 6 mm, history of stroke 11%).

Results:

	Atrial Fibrillation (845 pts)	Atrial Flutter (144 pts)
Left atrial thrombus	65 pts (7.7%)	6 pts (4.2%)
Spontaneous echo contrast	374 pts (44%)	30 pts (21%)*
Mild spontaneous echo contrast	63%	70%
Moderate spontaneous echo contrast	27%	27%
Severe spontaneous echo contrast	10%	3%

* $p < 0.05$

Conclusion: Pts with atrial fibrillation had 3 times more often a history of stroke (11% vs 3.5%) compared to pts with atrial flutter. TEE revealed left atrial thrombi and spontaneous echo contrast twice as often in pts with atrial fibrillation than in pts with atrial flutter (7.7% vs 4%).

1291 Does transoesophageal echocardiography before direct current cardioversion reduce the embolic risk in patients with atrial fibrillation

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Transesophageal echocardiography (TEE) has been proposed as a method of screening patients (pts) for left atrial thrombus before direct current cardioversion (CV), especially in pts without long term anticoagulation (AC). Aim of this prospective single center observational study was to evaluate the usefulness of TEE to reduce acute (48 hours) and subacute (4 weeks) thromboembolic events after CV in consecutive unselected pts with atrial fibrillation (AF) and effective AC (INR 2-3). Overall 1269 pts were registered. 193 pts were excluded, because of ineffective AC. Therefore 1076 pts were included in this study. A conventional approach to CV was performed during the first 2 years of the study (control phase 357 pts) followed by TEE guided approach to CV (719 pts).

Results: TEE revealed a left atrial thrombus in 55 pts (7.7%). If a thrombus was found, no CV was performed. The embolic events are listed below. No differences were observed in pts with and without embolic event. All pts with a thromboembolic event were therapeutically anticoagulated at least 3 weeks prior to CV. None of the pts, in whom CV was not performed experienced an embolic event. CV was successful in 86% of pts in the TEE group compared to only 78% in the conventional group.

Thromboembolic events after CV

	pts	Successful CV	Acute embolic events (48h)	Embolic events (4 weeks)	Bleeding
TTE	357	78%	0 pts	3 pts (0.8%)	0 pts
TEE	719	86%	2 pts (0.3%)	4 pts (0.8%)	2 pts (0.3%)
P-Value		0.001	n.s.	n.s.	n.s.

Conclusion: 1) TEE is useful in all pts before CV despite effective AC to exclude high risk pts. 2) Despite a normal TEE before CV, 6 pts had an embolic event, suggesting that CV itself might have a thrombogenic potential.

1292 High plasma von Willebrand factor levels predict future stroke, myocardial infarction and vascular death in 994 patients with atrial fibrillation

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Introduction: Atrial fibrillation (AF) is known to be associated with an abnormal prothrombotic state, but no plasma marker has yet been found to identify individuals at greatest risk of future thrombotic events.

Method: We measured plasma von Willebrand factor (vWf, an index of endothelial damage/dysfunction) and soluble P-selectin (sP-sel, an index of platelet activation) near study entry in 994 patients (mean age 69±9 years; 75% male) treated with aspirin (alone or with low inefficacious doses of warfarin) in the 3rd Stroke Prevention in Atrial Fibrillation (SPAF III) trial, and related levels of these markers to the incidence of first subsequent stroke, myocardial infarction (MI) or vascular death during the follow-up phase of SPAF III.

Results: Median vWf and sP-sel levels in the population were 145 (IQR 124-166) iU/dl and 32 (IQR 26-41) ng/ml, respectively. The composite endpoint 'stroke, MI or vascular death' occurred in 68 (6.8%) of the 994 patients during the follow-up period. 'High' (above median) levels of vWf were predictive of an increased risk of this endpoint (hazard ratio=2.8(95%CI=1.7-4.8),p<0.001, figure 1) and remained an independent predictor after adjusting for prior stroke, heart failure, hypertension, peripheral vascular disease, diabetes and age (p=0.004). sP-sel levels were not predictive of the composite endpoint (hazard ratio=1.3(95%CI=0.8-2.1), p=0.3).

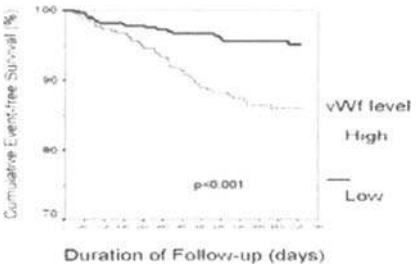

Figure 1: Kaplan-Meier survival curve.

Conclusion: Plasma vWf was an independent predictor of the combined endpoint of stroke, MI or vascular death in AF. sP-sel did not predict outcome. Endothelial damage/dysfunction appears more important than platelet activation in determining cardiovascular mortality and morbidity in AF. Plasma vWf may be a potentially useful marker for thromboembolic risk stratification in AF.

1293 Ximelagatran: a long-term oral direct thrombin inhibitor for stroke and systemic embolism prevention in nonvalvular atrial fibrillation patients

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Ximelagatran is a novel, oral direct thrombin inhibitor showing predictable dose-linear pharmacokinetics and no clinically significant food or drug-drug interactions. SPORTIF II was a 12-week, randomised, parallel-group study in patients with nonvalvular atrial fibrillation (NVAF) who had at least one additional risk factor for stroke (Petersen P. J Gen Intern Med 2001;16 (s1):164). Four groups of patients received either double-blind ximelagatran at doses of 20, 40 or 60 mg bid or warfarin aiming for an INR of 2.0-3.0. A total of 257 patients with a median age of 70 years (range, 39-95 years) were randomised and 254 received study drug (67 received warfarin and 187, ximelagatran). SPORTIF IV is an open-label 2-year follow-up of SPORTIF II in which eligible patients continued on ximelagatran 36 mg bid or warfarin. Since the start of SPORTIF II, ximelagatran has been given to 187 patients for the equivalent of 231 treatment years, and 67 patients have received warfarin for the equivalent of 76 treatment years. Following central adjudication, there have been two (0.9%) nonfatal ischaemic strokes in the ximelagatran group and two (2.6%) fatal haemorrhagic strokes in patients in the warfarin group. TIAs have been observed in one (0.4%) and two (2.6%) patients in the ximelagatran and warfarin groups, respectively. Major bleeds have been observed in two (0.9%) patients given ximelagatran and two (2.6%) patients treated with warfarin. No routine coagulation monitoring has been performed or required with ximelagatran. Five patients died in the trial including the two warfarin-treated patients who had strokes, while three patients died in the ximelagatran group, one from cardiac arrhythmia, one from a brain tumour and one from multiorgan failure due to old age. Asymptomatic S-alanine aminotransferase elevation was observed in a few ximelagatran-treated patients, but these levels decreased spontaneously during continued treatment or discontinuation of therapy. These preliminary data suggest that fixed-dose ximelagatran (36 mg bid) shows promise as an effective and well-tolerated oral anticoagulant for the prevention of stroke and systemic embolism, with no need for routine coagulation monitoring. Larger clinical studies to evaluate the effects of ximelagatran on the prevention of stroke in patients with NVAF are ongoing.

CARDIAC AND PERIPHERAL METABOLIC EFFECTS OF PACING

1294 Adverse effect of LBBB on regional myocardial oxygen consumption. Its reversal by electrical resynchronization evaluated by PET

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Background: Deterioration of left ventricle function in dilated cardiomyopathy (DC) is aggravated by asynchronous contraction induced by left bundle branch block (LBBB). Biventricular pacing (BIV) induces improvement of myocardial wall function, in patients affected by DC and LBBB, but, at the moment, the secondary changes on myocardial metabolism induced by BIV are unclear. The aim of our study was to evaluate the possible changes on myocardial metabolism and perfusion induced by BIV in these patients.
Methods: To this aim 12 patients (aged 60-79 yr, mean 69) affected by DC (III NYHA functional class and ejection fraction < 40%) and QRS duration above 150 ms, were submitted to cardiac PET in basal condition and 3 weeks after the implantation of a biventricular device (3 Insync 8040 Medtronic, 8 Contak TR and 1 Contak CD Guidant). Metabolism was evaluated using F18-fluorodeoxyglucose (FDG), by the glucose load-insulin technique, and perfusion by N13-ammonia (NH3), injected at rest. A visual and a semi quantitative analysis were performed, calculating by ROIs the septum to lateral uptake ratio (SLR). The myocardial blood flow (MBF) was also calculated in ml/min/g using a dynamic acquisition and a modified Patlak method.
Results: In all the 12 patients a selective defect in FDG uptake in the septum was present in basal condition (mean SLR 0.59±0.16) with a "reverse mismatch" effect in comparison with NH3 (mean SLR 1.04±0.18, p=0.005). During BIV the distribution of FDG in the septal area improved (mean SLR 0.91±0.18 p=ns); on the contrary no significant changes were found in NH3 uptake (mean SLR 0.99±0.19). Mean ejection fraction increased from 32±6 to 41±5 (p=0.007). At the quantitative analysis the mean MBF in the septum did not show variations in basal condition and during BIV (0.81±0.32 vs 0.79±0.16; p=ns).
In conclusion, our experience suggests that, in patients affected by DC and LBBB, BIV could improve the septal glucose metabolism without significant changes in the myocardial blood flow. This phenomenon is probably due to resynchronizazion of the contraction of the septum.

1295 Biventricular pacing and blood flow in great arteries: ventricular resynchronisation alters electro-mechanical coupling of both ventricles

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The improvement of parameters of systolic and diastolic function of left ventricle induced by biventricular pacing (BVP) is considered to be a consequence of better-coordinated and earlier left ventricular contraction. To test this assumption, the timing of ventricular outputs derived from intervals between the onset of ventricular depolarisation (surface QRS) and Doppler assessed onset (O) and peak (P) of blood flow (BF) in aorta (AO) and pulmonary artery (PA) were compared before and after BVP.
Clinical parameters and echocardiography were prospectively followed-up in 13 patients with MUSTIC indications for BVP for 6 months after implant (7 males; 58.6±10.5 year old; 7 idiopathic, 4 ischaemic, and 2 other cardiomyopathies). NYHA class, 6-minutes corridor walk, quality of life questionnaire, and echocardiographic parameters were significantly improved over the entire period of follow-up (FU).
At the baseline, O and P of BF in AO were dealyed in comparison to those in PA by 65 and 73 ms respectively. This delay was corrected with BVP to 13 and 18 ms at 1 month, 5 and 15 ms at 3 months, and 1.5 and 3 ms at 6 moths of FU. Surprisingly, this improvement resulted not only from an earlier O and P of BF in AO (by 35 and 32 ms, 30 and 20 ms, and 35 and 26 ms respectively) but also from a delayed O and P of BF in PA that were deferred by 18 and 22 ms at 1 month, 30 and 38 ms at 3 months, and 30 and 45 ms at 6 moths of FU with BVP.
In conclusion, the synchronisation of outputs of left (LV) and right (RV) ventricles due to BVP results not only from an earlier contraction of LV but also from a deferred contraction of RV. This finding suggests that the effect of BVP is derived from an alteration of inter-ventricular electro-mechanical coupling.

1296 Impact of asynchronous ventricular activation sequence on cytokine activation and oxidative stress in paced patients

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Background: Asynchronous ventricular activation due to permanent pacing through the right ventricular apex results in functional and structural changes, reduced oxygen consumption and disturbances of fatty acid metabolism. The aim of our study was to examine the uninvestigated role of abnormal ventricular activation on the oxidative stress (serum lipid peroxidation), serum levels of interleucin-6 (IL-6) and tumor necrosis factor-a (TNF-a) in paced patients.
Methods: We included 10 patients (6 men, aged 57 ± 7 years) with sick sinus syndrome, in whom a permanent dual-chamber rate-adaptive (DDDR) pacemaker was implanted. All patients had a normal echocardiogram and coronary angiogram. The pacemaker was initially programmed as AAI with a basic rate of 40 bpm. In a crossover design three months later, the patients were randomized for 15 days to either AAI or DDD pacing, with a basic rate of 60 bpm. During DDD pacing, the ventricular capture was completely paced. At the end of each 15-day randomization, blood samples were taken to evaluate lipid peroxides (measured by TBARBS assay), IL-6 and TNF-a (determined in plasma by high sensitivity immunoassays). Before randomization, the same markers were evaluated following 1 hour of AAI and 1 hour of DDD pacing, in a random order.
Results: One hour AAI and DDD pacing marker values showed no significant differences (Lipid peroxides: 254 ± 113 μmol/l, TNF-a: 2.4 ± 0.9 pg/ml, IL-6: 1.9 ± 0.5 pg/ml in AAI compared to 277 ± 107 μmol/l, 2.2 ± 0.69 pg/ml, 2.4 ± 0.8 pg/ml respectively in DDD, p:NS). However lipid peroxides and IL-6 levels were significantly lower, following the 15-day AAI pacing period compared to the DDD pacing period (Lipid peroxides: 369 ± 134 μmol/l, IL-6: 3.6 ± 1.2 pg/ml in AAI compared to 489 ± 114 μmol/l, 4.8 ± 1.6 pg/ml respectively in DDD, p<0.05). TNF-a revealed no significant change (3.1 ± 1,1 pg/ml in AAI versus 3,4 ± 0.9 pg/ml in DDD, p:NS).
Conclusions: Patients with asynchronous ventricular activation sequence caused by right ventricular apex pacing, showed increased cytokine activation and oxidative stress levels after a short-term period of continuous pacing. The clinical importance of these findings deserves further investigation.

1297 Cardiac resynchronization therapy improves myocardial perfusion and glucose metabolism in heart failure patients with left bundle branch block

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Patients (pts) with heart failure (HF) and left bundle branch block (LBBB) present an asynchronous left ventricular (LV) activation resulting in early contraction of the septal wall (SEP) and late contraction of the lateral wall (LAT). This might lead to a reduced glucose (GLC) metabolism and a reversed perfusion/metabolism mismatch of SEP. Cardiac resynchronization therapy (CRT) recoordinates LV activation; thus normalization of the perfusion/metabolism abnormalities associated with LBBB may be another mechanism for improved LV hemodynamics in these pts.
Methods: In 12 pts (9f, 3m, 62±12y) with LBBB (QRS 170±24ms), HF (EF 27±7%, NYHA II 2 pts, NYHA III 10pts) and dilative cardiomyopathy a pacemaker for CRT (VDD mode) was implanted. Attenuation corrected 99mTc-MIBI-SPECT (MIBI; Solus, ADAC Labs.) and gated 18-FDG-PET (FDG; ECAT EXACT 922/47, Siemens CTI) were performed before (basal) and after 14±2 days of CRT. Relative MIBI and FDG uptake [%] of SEP, LAT, anterior (ANT) and posterior (POST) left ventricular wall were quantified semiquantitatively in a total of 25 myocardial segments.
Results: Short-term effects of CRT on relative MIBI and FDG uptake are shown in the table.

Effects of CRT on MIBI and FDG uptake

		ANT (%)	POST (%)	LAT (%)	SEP (%)	LAT/SEP
MIBI	Basal	69±13	73±11	83±6	67±12	1.28
	CRT	74±15*	76±11	81±9	72±13*	1.15*
FDG	Basal	65±15	68±10	87±7	53±14	1.77
	CRT	72±12	74±10*	77+/9*	69±16*	1.16*

Mean ± SD; *p<0.05 vs basal

Conclusion: Pts with LBBB and HF have a slightly reduced ANT-SEP MIBI and a more severely reduced SEP FDG uptake (SEP reversed perfusion/metabolism mismatch). CRT leads to a normalized ANT-SEP perfusion and SEP metabolism with suspension of the septal reversed mismatch, paralleled by a relative decrease in LAT metabolism. Thus, hemodynamic benefit of short-term CRT may be partly explained by a normalized LAT/SEP perfusion and metabolism ratio with a redistribution from LAT to SEP.

1298 Myocardial perfusion and metabolic changes induced by right and biventricular pacing: evaluation by positron emission tomography

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Aim of the study: Evaluate the possible changes on myocardial metabolism and perfusion induced by right ventricular pacing (VVI or DDD) and biventricular pacing (BIV) in patients affected by dilated cardiomyopathy (DC).
Methods: 28 patients (pts), age 48-79, mean 66, affected by dilated cardiomyopathy were submitted to cardiac Positron Emission Tomography (PET) for evaluation of myocardial viability. 6 pts had a VVI or DDD pacemaker implanted for conventional reasons (gr.A), 12 pts had a BIV, implanted for the presence of left bundle brach block (LBBB) and a QRS duration above 150 ms (gr.B), while the other 10 pts, without pacemaker or LBBB, were considered as controls (Gr.C). All the pts were in III NYHA class and had an EF<35%. None of them presented critical coronary stenosis. Metabolism was evaluated by PET using F18-fluorodeoxyglucose (FDG), by the glucose load-insulin technique, and perfusion by N13-ammonia (NH3), injected at rest. A visual and a semi quantitative analysis were performed, calculating by ROIs the septum to lateral uptake ratio (SLR).
Results: In Gr.A a selective defect in FDG uptake in the septum was present (mean SLR 0.67±0.15, p<0.01 in comparison with Gr.C (0.95±0.10), with a "reverse mismatch" effect in comparison with perfusion (NH3 uptake: Gr.A mean SLR 1.01±0.21; Gr.C 0.94±0.11, p=ns). Gr.B presented a homogeneous distribution of FDG and NH3 in the myocardial wall of both FDG and NH3 (respectively mean SLR 0.91±0.18 and 0.99±0.17, p=ns in respect to Gr.C).
Conclusions: Our experience could suggest that, in patients affected by dilated cardiomyopathy, conventional right pacing induce interference in the metabolism of the septum not correlated to changes in the perfusion, but probably due to asynchronous contraction of the septum. On the contrary biventricular pacing does not modify the myocardial metabolism and perfusion suggesting a better synchronized contraction of left ventricle.

1299 Alterations of cardiac metabolism induced by biventricular pacing in patients with heart failure

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Introduction: The synchronisation of ventricular contraction in CHF patients by biventricular pacing (BP) has shown to improve contractility with no increase of myocardial oxygen consumption. Alterations at energetic metabolism induced by BP were never studied previously although they constitute the essential background for the improvement of cardiac function.
Aim: We studied cardiac metabolism (in terms of percentage myocardial extraction of glucose, pyruvate, lactate and NEFA) in six patients with heart failure (age 71±12 year; EF% 26.75±2.4; VO2 peak 8.6±2.1 ml/kg/min) before and after BP (10 min of acute stimulation).
Methods: The patients were implanted with biventricular system Guidant Cont@kt TR or CD with catheter in coronary sinus Easy-Track. Two additional catheters were positioned in the coronary sinus and in aorta, respectively, in order to simultaneously draw blood for metabolic measurements.
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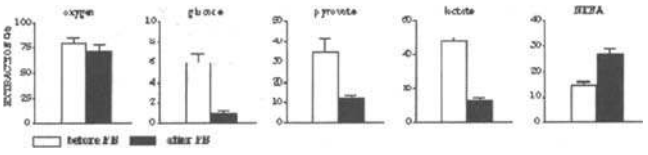
Results: Our data show that BP does not increase the percentage of oxygen extraction, while results in a clear redistribution of the used substrates by myocardium: it reduces the extraction of carbohydrates and increases that of NEFA, a more physiologic and convenient substrate in terms of energetic need.



Conclusions: Our preliminary data indicate that BP results in a metabolic shift in favour of NEFA without negatively affecting O2 consumption: in energetic terms, this results in a higher ATP availability that may be useful to improve cardiac function.

PREVENTION, DIAGNOSIS AND INTERVENTION: THE IMPACT OF NURSING IN PATIENT CARE

1305 Contribution of nursing to risk factor management as perceived by patients with established coronary heart disease

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Background - Guidelines stress the importance of patient education in risk factor management in patients with coronary heart disease (CHD).
Aims - To evaluate whether guidelines on patient education in risk factor management are followed in clinical practice and to assess the contribution of nursing to risk factor management as perceived by patients with established CHD.
Methods - At 3 Dutch hospitals, 357 consecutive patients were identified after a first coronary-artery bypass graft, first percutaneous transluminal coronary angioplasty or hospital admission with acute myocardial infarction or ischaemia. Data were collected through patient interviews at least 6 months (median = 20 months; IQR = 15 - 26 months) after hospital admission. Smoking was defined as self-reported or > 10 ppm carbon monoxide in breath; overweight as Body Mass Index >= 25 kg/m^2; hypertension as >= 140/90 mmHg, high cholesterol >=5.0 mmol/L, and sedentary lifestyle as self-reported no or only light physical activity in most weeks.
Results - Among smokers (104, 29%), overweight patients (276, 78%), patients with hypertension (185, 52%), high cholesterol (151, 42%), or sedentary lifestyle (207, 58%), 75%, 36%, 65%, 61%, and 49%, respectively, reported that information on the presence or management of their risk factor(s) was provided. Chi-square test showed that patients with acute myocardial ischaemia were the most poorly informed (p=0.02) Among the informed patients, the proportion of patients informed by nurses ranged from 14% (lowering cholesterol) to 23% (increasing physical activity), while 55% (lowering cholesterol) to 71% (stop smoking) were informed by physicians, and the percentage of patients informed by an other caregiver ranged from 24% (stop smoking) to 45% (losing weight).
Conclusion - Although guidelines stress the importance of patient education in secondary prevention, many patients with established CHD and cardiovascular risk factors do not remember ever having received information about the presence or management of their risk factors. The contribution of nurses to risk factor management appeared to be small compared to the input of physicians and other caregivers. If risk factor management is considered to be a responsibility of nurses, current nursing activities in this area should reflect this concern. Identification of patients at risk and long term follow up need to be improved, which may be possible through nurse-led prevention clinics or provision of secondary prevention as part of a comprehensive cardiac rehabilitation programme.

1306 Does early percutaneous coronary intervention strategy affect patient disability and return to work after an acute coronary syndrome?

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Background and aims: Current management of acute coronary syndromes (unstable angina pectoris, non-ST elevation infarction)(ACS) includes in many pts early revascularization by percutaneous coronary intervention (PCI). Little attention has been directed to the effect of an early interventional strategy on perceived pt disability, lifestyle modification and return to work after ACS.
Patients: Structured anonymous questionnaire was completed and returned by 70 of 78 consecutive pts (age 41-90 yrs; 47 males, 23 females) 6-12 mths after hospitalization for ACS. Early PCI (during index hospitalization) was performed in 21/70 pts according to symptoms and preference of treating physician.
Results: Hospitalization for ACS impacted adversely on pt perception and self-image, with more than half seeing themselves as "heart pts" thereafter. Changes in perception and self-evaluation were less marked in pts undergoing early PCI strategy. Half the pts undergoing PCI returned to work, only a third of the non-PCI group. Diagnostic angiography without PCI (N=43) had no effect on any measure of perceived disability or return to work.

Early PCI and perceived disability

	Age (yrs)	"Heart pt" perception	Increased dependency on others	Decreased self-confidence	Return to work
Early PCI (N=21)	65+13	12 (57%)	6 (29%)	8 (34%)	5/10 (50%)
No PCI (N=49)	66+10	35 (71%)	24 (49%)	33 (67%)	9/25 (36%)
p value	0.71	0.37	0.18	0.04	0.15

Conclusions: In pts with ACS who underwent early PCI (during index hospitalization): 1. There was less change in perceived pt disability and self-confidence after discharge, 2. More pts tended to return to work. 3. The advantage of PCI during index admission on pt lifestyle and return to work strongly supports an early aggressive strategy in pts hospitalized for ACS.

1307 Six minute walking test early after cardiac surgery in septuagenarian patients

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In quality-of-care assessment of post cardiac-surgery rehabilitation programs, measures of functional recovery have been proposed as outcome indicators. Aim of the study was to evaluate feasibility, safety and informative content of a 6-min walking test performed early after admission to an in-hospital rehabilitation unit (R) in over-70 pts.

Methods 107 consecutive elderly pts (74±4 yrs) admitted to R 12±5 days after surgery (53 CABG, 36 valve surgery, 18 combined) performed within 7 days a 6-min walking test (WT1), on telemetry monitoring; in 97 WT1 was feasible within 4 days. The recorded variables were: resting and exertional heart rate, score of fatigue (Borg Scale 1-20), symptoms, ECG alterations and arrhythmias. Other variables were: comorbidity (Charlson index), length of stay and complications in the whole surgical and R stay, disability (nursing needs: Maslow/nursing chart), functional status at discharge (WT2), left ventricular EF (LVEF), number of training sessions, self-perceived health-status (Euroqual questionnaire: Eq1 at entry, Eq2 at discharge).

Results The mean walked distance was 194±93m at WT1 and 286±106m at WT2, p<.0001; no complication and ECG alteration occurred; only isolated premature beats were recorded in 26 pts. Heart rate increased from 86±13 at rest to 95±17 bpm (p<.0001).The perceived fatigue was 12.9±1.2 Borg.
The significant differences between pts who performed WT1 within 4 days or later, and between pts who walked ≤120m (lower quartile) or more are reported in the table.

	<=4 days (n 10)	>4 days (n 97)	>120 m (n 79)	<=120 m (n 28)
Complications-n	1.7±1.5	3.7±1.4 **	1.7±1.4	2.5±1.9 *
Length of surgery stay	11.8±4.3	17±8.9 **		
Total length of stay	30.9±8.5	37.1±16 *		
Nursing needs-n	0.9±1	2.9±1.9 **	0.8±1	1.6±1.5 *
Eq1	49.9±20	34.5±23 *	52.3±18	36.7±22 **
WT2-m	297±103	182±83 **	211±93	113±98 **

* p<0.01, ** p<0.0001

LVEF, training sessions and Eq2 did not differ between the groups.

Conclusions In elderly pts after cardiac surgery a 6-min walking test performed within the first week of entry in R is feasible and safe. Simple cut-offs like timing of the test and walking performance identify more severe pts with lower susceptibility to recovery.

1308 Cardiac nurse led echocardiography – Using portable devices

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Introduction: Echocardiography is the commonest non invasive way to assess cardiac function providing vital diagnostic and prognostic information. Cardiac technicians are unable to provide this service in the evenings and over weekends and have many requests to deal with. We assessed whether cardiac nurses with no experience of practical echocardiography could be given training and be asked to interpret left ventricular (LV) systolic function in hospital patients.

Methods: 2 cardiac nurses with no previous echocardiographic skills were given 2 half day teaching sessions in performing and interpreting cardiac ultrasound. Echocardiograms were then performed on 50 patients using portable machines. LV systolic function was to be defined as normal or as mild, moderate or severe impairment. The nurses were also asked if they would recommend a further study. An experienced cardiac technician repeated the study within 24 hours.

Results: 50 patients were studied and of these 34 (68%) were male and 16 (32%) were female. The average age of each patient studied was 64. Assessment of LV function as normal or abnormal was correct in 43 (86%) of all patients. The assessment of normal left ventricular function was correct in 33 out of 37 patients (89%) and assessment of abnormal LV function was correct in 10 out of 13 patients (77%). Quantification of impaired LV function was correct in 5 patients and incorrect in 5. A full study was recommended in 24 of these patients, because of impaired function in 14, limited views in 9, dilated LV in 2 and a pericardial effusion in 1. A full study was not recommended in 2 patients when one was required – impaired LV was called normal in both cases.

Conclusions: Cardiac nurses who provide 24 hour care for patients can perform echocardiographic assessment of left ventricular function accurately in the majority of cases, given appropriate background and training in echocardiography. Cardiac nurses recommended further studies on appropriate patients. This multi-disciplinary approach with nurse led echocardiography has the benefit of triaging requests and streamlining services.

1309 The European heart failure self-care behaviour scale: ready to use!

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Background: Improvement of self-care behaviour is an aim of several non-pharmacological nurse led management programs for patients with heart failure (HF). These programs are often evaluated on effects on readmission, costs and quality of life. It is, however, also important to know how patients changed their self-care behaviour as a result of such a program. Therefore a comprehensive, reliable and valid measure of the self-care behaviour of HF patients is needed..

Objectives: To develop a scale measuring the behaviour that HF patients perform to maintain life, healthy functioning, personal development and well being.

Method: The European Heart Failure Self-Care Behaviour Scale (EHFScBS) was developed in three phases:
1] concept analysis and first construction by literature review, by an international panel of experts and pilot testing in 179 HF patients
2] weighing and selecting items by 10 HF nurses and an international expert panel and changing scoring format from dichotomous to Likert scaling
3] testing of the new scale for validity and reliability in a sample of 442 cardiac patients from six European centres, both hospital and primary care.

Results The European Heart Failure Self-Care Behaviour Scale is a 12 item, self-administered questionnaire (Likert scale) that covers items concerning self-care behaviour of HF patients. The items covered concern for example daily weighting, fluid restriction, diet, exercise or contacting a health care provider. Face-validity and concurrent validity of the scale was established and the internal consistency of the scale was tested using pooled data of 442 patients from two centres in Sweden, three in the Netherlands and one in Italy. Cronbachs's alpha ranged in the different HF samples from 0.67 to 0.93 and was 0.81 in the total sample

Conclusion: The EHFScBS is a valid, reliable and practical scale to measure self-care behaviour of heart failure patients. It is ready to use in various studies evaluation the outcome of non-pharmacological management programs.

1310 Effects of follow-up after hospitalisation at a nurse-led heart failure clinic: a randomiced trial

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Chronic heart failure is a huge public health problem with poor prognosis and frequent hospital admissions. Patients are often discharged from hospital without optimised treatment and sufficient patient education, and therefore at high risk for readmission if not optimal follow up is provided. The aim of this prospective study was to evaluate the effect of follow up at a nurse-led heart failure clinic on event-free survival,self-care behaviour and health-related quality of life for patients hospitalised due to heart failure.

Methods: A total of 106 patients were randomly assigned to either the intervention group (n=52) with follow up at a nurse-led heart failure clinic or to the control group (n=54) receiving follow up in primary health care. Mortality and morbidity were collected from medical records. Quality of life was measured through Short-Form 36 and Minnesota Living with Heart Failure Questionnaire. Self-care behaviour was measured through Heart Failure Self-Care Behaviour Scale.

Results: The majority of the patients in the intervention group paid one visit to the nurse-led heart failure clinic (n=28), 12 patients paid two visits and the rest of the patients 3-8 visits. In total the intervention group had 84 visits.
There were fewer patients with events (death or admission) after 12 months in the intervention group compared to the control group (29 versus 40, P = 0.03) and fewer deaths after 3 months (3 versus 13, P = 0.009) and 12 months (7 versus 20, P = 0.005). The intervention group also had fewer admissions (33 versus 56, P = 0.047) and days in hospital (350 versus 592, P = 0.045) during the first 3 months. After 12 months there was a trend towards fewer hospital admissions (P = 0.06) and significantly fewer days in hospital (P = 0.02)in the intervention group. The intervention group had significantly higher self-care scores at 3 and 12 months compared to the control group (P = 0.02 and P = 0.01). Both groups improved their self-care behaviour after 3 months (P < 0.001 and P = 0.01), but only the patients in the intervention group retained the improved self-care behaviour after 12 months (P < 0.001). There were no significant differences between the groups regarding quality of life. Quality of life data has not been adjusted for the large difference in mortality between the groups.

Conclusion: Follow up after hospitalisation at a nurse-led heart failure clinic can improve event-free survival and self-care behaviour in patients with heart failure as well as reduce the number of readmissions and days in hospital.

PERCUTANEOUS INTERVENTIONS IN VALVULAR HEART DISEASE

1311 Temporal trends in percutaneous mitral commissurotomy over a 15-year period from a series of 2538 patients

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The analysis of a large single-center series of patients who underwent percutaneous mitral commissurotomy (PMC) for mitral stenosis provides information regarding the evolution of the indications and results of the technique over time. From 1986 to 2000, 2538 consecutive patients underwent PMC in our institution. There were 30 cases of technical failure. Initially, a single balloon was used in 30 patients, then a double-balloon in 586, and finally the Inoue stepwise technique with echo monitoring in the remaining 1892 patients, after October 1990. Patients' characteristics and results were analysed each year and globally compared using analysis of variance.

From 1986 to 2000, mean age increased from 43±15 to 51±15 yrs ($p<0.0001$) and the percentage of patients in NYHA class I or II before PMC increased from 17 to 48% ($p<0.0001$). Valve anatomy was assessed by echocardiography and classified in 3 groups: pliable valves and mild subvalvular disease (Group 1), pliable valves and severe subvalvular disease (Group 2), and calcified valves confirmed by fluoroscopy (Group 3). The percentage of patients in Group 1 decreased from 33% to 4% between 1986 and 2000, while it increased from 40 to 64% in Group 2, and from 26 to 32% in Group 3 ($p<0.0001$). There was no significant variation in mitral valve area, with a mean value of 1.03±0.23 cm^2 ($p=0.18$).

Technical failure decreased from 6% in 1986-87 to 4% in 1988 and 0.7% for following years ($p<0.0001$). The incidence of tamponade decreased from 1.4% in 1986-87 to 0.1% for following years ($p<0.001$).

The proportion of good immediate results, defined as a valve area $>=1.5cm^2$ with no regurgitation >2/4 did not differ over time, with a mean value of 87% ($p=0.20$).

In conclusion 1) Over this 15-year period, candidates for PMC were getting older and had a less favourable valve anatomy, but underwent PMC at an earlier functional stage of their disease. 2) These results confirm the importance of experience in the dramatic reduction of the frequency of technical failure and hemopericardium. 3) Despite the less favourable characteristics of the patients, the success rate remained high and stable.

1312 Immediate and short-term effects of graded dilatation for severe mitral stenosis with moderate mitral regurgitation using the inoue balloon

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Aim: To study the safety as well as the immediate and short term results of graded Inoue balloon valvotomy in patients with severe mitral stenosis associated with moderate mitral regurgitation, with special emphasis on the changes that occur in the degree of mitral regurgitation and functional class post-valvotomy.

Methods: 15 patients (60% females, 40% atrial fibrillation) with severe symptomatic mitral stenosis (mitral valve area (MVA) < 1.2 cm^2, NYHA more than or equal functional class (Fc)II, Echo score 7.4 ± 1.5) and mild to moderate mitral regurgitation (mitral regurgitant jet area (MRJA) between 3 and 7 cm^2 by Doppler colour flow mapping) were subjected to graded balloon mitral valvotomy. All patients were assessed as regards their NYHA functional class, treadmill exercise duration, and a detailed echocardiographic study before, and immediately after graded dilatation of the mitral valve as well as at 3-6 months follow-up.

Results: See table.

	Predilatation	Post dilatation	Follow-up (FU)	p-value Pre vs FU
Functional class (>Fc II, %)	73	–	13	< 0.001
Exercise duration (min)	4.7 ± 3.5	–	10.6 ± 4.1	0.0036
MVA (cm^2)	0.91 ± 0.15	1.95 ± 0.32	1.75 ± 0.22*	<0.001
MRJA (cm^2)	4.44 ± 0.65	6.74 ± 2.65	7.93 ± 3.21*	<0.001
LVEDD (cm)	5.1 ± 0.5	–	5.1 ± 0.6	NS
Left atrium (cm)	5.4 ± 0.6	–	5.2 ± 0.5	NS

* p post vs follow-up: insignificant

Conclusion: Graded dilatation of severe mitral stenosis associated with moderate mitral regurgitation is associated with a significant gain in mitral valve area which causes a marked improvement in functional class and treadmill exercise duration. However, it is associated with increase in the degree of mitral regurgitation, but this increase is well tolerated in all patients. The favorable haemodynamic effects are maintained over the short-term follow-up period. Thus, in these patients, who were routinely sent to surgery, mitral valve repair or replacement can be deferred to a later date or even indefinitely.

1313 Long-term follow-up results of mitral balloon valvuloplasty (12 years) and predictors of restenosis

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Background: The long-term results of mitral balloon valvuloplasty (MBV) are not well characterized.

Methods: We analyzed the results of 362 patients from mitral balloon database in our hospital. These patients had clinical and echocardiographic follow-up studies 1-12 (mean 5 1) year after MBV. The morphologic features of the mitral valve were graded and semiquantitated using Wilkin's mitral echo score (MES), patients were divided into 2 groups according to MES at the time of valvuloplasty, group A (MES less than or equal to 8) and group B (MES > 8). Comparison of hemodynamic variables was done using student t-test. Chi-square/Exact-test was used to study categorical variables. Logistic regression analysis was used to identify predictors of restenosis. Event free survival was plotted using the Kaplan Meier test.

Results: The procedure was successful in 98% of cases and no death was encountered. The immediate and long-term hemodynamic results are as follows (see table).

	Group A (n=274)	Group B (n=88)	P Value
Age	31 ± 10.9	34 ± 11.2	P < 0.05
MVA before cm^2	0.9 ± 0.16	0.9 ± 0.19	P = 0.2
MVA immediate cm^2	2.00 ± 0.3	1.8 ± 0.27	P < 0.0001
MVA follow-up cm^2	1.8 ± 0.36	1.5 ± 0.38	P < 0.0001
Restenosis	32 (12%)	22 (25%)	P < 0.001

Restenosis in all patients is 15%.

Logistic regression analysis identified MES and post procedure MVA < 2.0 cm as strong predictors of restenosis ($P < 0.0001$ and $P < 0.05$ respectively). The event free survival for 1, 4, 6, 8, 10, 12 years was 0.99, 0.96, 0.92, 0.82, 0.64, 0.58 for group A and 0.98, 0.8, 0.74, 0.54, 0.3, 0.15 for group B respectively.

Conclusions: Good results were observed up to 12 years after MBV and unfavorable MVM (MES > 8) and post procedure MVA < 2.0 cm are powerful independent predictor of restenosis.

1314 Long-term effect of successful mitral balloon valvotomy on severe tricuspid regurgitation

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Background: Significant tricuspid regurgitation (TR) secondary to severe pulmonary hypertension (PH) is frequently associated with severe mitral stenosis (MS) and it has adverse impact on morbidity and mortality in pts undergoing mitral valve surgery. The effect of successful mitral balloon valvotomy (MBV) on significant TR is not fully elucidated.

Methods: 559 pts with severe MS underwent MBV over 12-year period, of these 76 pts had significant TR (2 to 4+). The TR was evaluated by Doppler echo before MBV and at follow-up 1-12 (mean 5 1) years and graded on scale 1 to 4. The pts were divided into group A (59 pts) in whom TR regressed by 3 one scale and group B (17 pts) TR did not change.

Results: In 59 pts TR regressed or disappeared due to regression of pulmonary hypertension. 12 out of 20 pts with severe TR (3 to 4+) regressed to 0 to 1 TR.

Measurement	Group A (59 pts)	Group B (17 pts)	P value
Age	29 ± 12	35 ± 12	0.13
MVA area cm^2 (B)	0.8 ± 0.16	0.8 ± 0.17	0.24
(I)	1.8 ± 0.34	1.8 ± 0.27	0.32
(F)	1.6 ± 0.45	1.5 ± 0.27	0.23
PAP mmHg (B)	62 ± 19	51 ± 14	<0.05
(F)	34 ± 15.0	41 ± 7.6	0.01
TR (B)	2.4 ± 0.55	2.1 ± 0.33	<0.05
(F)	0.86 ± 0.60	2.6 ± 0.8	<0.0001

B=before; I=immediately after MBV; F=follow-up; MVA=mitral valve area; PAP=pulmonary artery pressure; TR=tricuspid regurgitation

Conclusions: (1) Regression of significant TR after successful MBV was observed in the majority of pts who had associated severe pulmonary hypertension, and (2) MBV should be the treatment of choice even in the presence of severe TR secondary to pulmonary hypertension.

1315 Immediate and late outcome of newborn babies following balloon mitral commissurotomy during pregnancy

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Balloon mitral commissurotomy (BMC) during pregnancy proved effective and safe with regard to the fetus and mother outcome up to the delivery time. However, some concern remains about potential late side effects of radiation in the newborn babies.

Methods and Results: From 06/90 to 06/2000, 58 pregnant women with severe mitral stenosis underwent a successful BMC at 26 (14-37) weeks of gestation. Mean fluoroscopy time was 16±7 min. All pts delivered at full term: 55 vaginally and 3 (5%) by caesarian section for obstetrical reasons. None of the 59 (1 twin pregnancy)newborn babies had a malformation. Mean body weight at birth was 3.04 ± 0.45 (1.8-4.4) kg. Hypotrophy (weight < - 2 SD) was observed in 4 of them. Apgar score was > 9 in all of them.

At a mean follow-up of 71 ± 35 (8-120) months, 45 (76%) babies were evaluated physically and mentally.

Physical growth was evaluated by the determination of height, weight and head circumference compared to the normal curves. Mental development was assessed by the determination of the intelligence quotient (IQ) by a pediatric psychologist.

At follow-up, a physical malformation was observed in none of the babies. Height, weight and head circumference were within ±2 SD in all of them. A normal IQ (> 0.8) was observed in 39 (87%) of them.

In the remaining 6 pts, there was no major mental retardation with an IQ between 0.52 and 0.7.

Conclusion: The immediate and late clinical outcome of newborn babies following balloon mitral commissurortomy is excellent with no evidence of radiation side effects up to six years of follow-up.

1316 Immediate results of non-surgical implantation of a balloon-expandable prosthetic valve: an experimental study in sheep

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In patients with severe valvular disease and contra-indication to surgery, a balloon-expandable prosthetic valves (BEPV) might offer a new potential therapeutic option in the next future. In this study, we assessed the feasibility of non surgical implantation of an original BEPV, a three-leaflets foldable valve made of polyurethane or bovine pericardium, mounted inside a vascular tubular stainless steel stent. BEPV was crimped over a balloon catheter of 23 to 25 mm in diameter and 40 mm in length. This delivery catheter was pushed over a 0.035 stiff guide wire, through a 22 to 24-Fr sheath introduced after cut-down into the right carotid artery or the right jugular vein (according to the selected implantation site). BEPV was delivered at the desired site by high pressure balloon inflation. Implantations were performed at the following sites under general anesthesia in 48 sheep weighing 30 to 60 kg: descending aorta in 5, ascending aorta in 2, within the native aortic valve (AoV) in 19 and within the native pulmonary valve (PV) in 22. Before implantation, vascular diameters were calculated by selective angiography using the introducer sheath as a reference and by 2-D trans thoracic echocardiography in the last 20 cases. After implantation, repeat angiograms were performed near the BEPV ends to assess the antegrade and retrograde flow; the pressure gradient across BEPV was measured and the valvular function was assessed in the 25 last cases using 2D and TEE Echocardiography and Doppler. BEPV could be successfully delivered at the selected implantation site in all but 3 cases (immediate migration: AoV=2; PV=1). Early death (within 3h) occurred in 6 AoV cases, related to a wrong BEPV positioning in 3 (below the native valve, with subsequent severe mitral valve dysfunction and/or aortic regurgitation) and to pharmacological cause in 3, and in 1 PV case (ventricular fibrillation). Delayed (within 6h) BEPV migration occurred in 2 AoV and 2 PV. After successful implantation, the transvalvular gradient was minimal (< 10 mmHg) and there was no or mild regurgitation. Valvular motion was normal in the 2 AoV and 20 PV controlled by Echocardiography and Doppler. Conclusions: This BEPV can be successfully implanted in sheep in the aorta or within native valves, leading to excellent and promising acute hemodynamic results. Improvements of BEPV components and increased technical experience have markedly decreased the incidence of wrong positioning and early migration and a chronic experiment is currently ongoing.

ENDOGENOUS MECHANISM IN MYOCARDIAL PROTECTION

1340 Myocyte survival against calcium overload or simulated ischaemia is improved by overexpression of the stress and calcium-binding protein GRP94

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Increase of free intracellular calcium ions $[Ca^{2+}]_i$ plays an important role in pathogenesis of cardiomyocyte injury after ischemia-reperfusion. We investigated whether the glucose-regulated protein GRP94, a stress- and calcium-binding protein localized in cardiac sarcoplasmic reticulum, is involved in protection of myocytes exposed to calcium overload and simulated ischemia. GRP94 overexpression was achieved in skeletal C2C12 and heart H9c2 muscle cell lines by stable transfection and in neonatal rat ventricular myocytes by transient transfection with constructs expressing GRP94. Quantitative analysis revealed a 3 to 8 fold increase of GRP94 in five different GRP94 overexpressing clones with minor increase in GRP78 or calreticulin content. Calcium overload was obtained by exposing control and GRP94 overexpressing clones to 2.5μM A23187 and cell damage was evaluated by determination of LDH enzymatic activity released in culture medium and retained in cell pellets. Results show that every GRP94-overexpressing clone studied displays a significantly higher intracellular retention of LDH (from + 29.3% to +57.5%), indicating prolonged cell viability. Kynetic analysis of $[Ca^{2+}]_i$, performed in C2C12 control and GRP94 overexpressing clones, showed a significantly lower Fluo-3 fluorescence during the first 10 min after exposure to A23187 of GRP94 overexpressing clones with respect to control clones. Propidium iodide uptake was used for evaluation of GRP94 protective effect on neonatal rat cardiomyocytes transfected with a construct co-expressing GRP94 with the green fluorescent protein GFP: a lower percentage of necrotic propidium-iodide positive/GFP fluorescent myocytes expressing exogenous GRP94 was observed after exposure to the ionophore with respect to myocytes transfected with GFP alone (6.6% vs 14.0%, respectively). A comparable protective effect was detected when transfected neonatal cardiomyocytes were exposed for 4 hours to anoxia in the presence of ischemic buffer (Zhao et al. J Biol Chem 273, 23072, 1998): only 8.5% of GRP94 overexpressing/GFP positive cardiomyocytes were necrotic/propidium iodide-positive with respect to 17.7% of control/GFP positive cardiomyocytes. In conclusion, increase in GRP94 expression protects myocytes from necrosis induced by ischemia and calcium overload, where it delays the increase in $[Ca^{2+}]_i$, presumably through its involvement as a calcium-binding protein.

1341 Activation of p38 MAPK is not a trigger for ischaemic preconditioning

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The role of the activation of p38 MAP kinase (MAPK) as trigger of ischemic preconditioning (PC) is controversial. Bracketing the preconditioning event with the p38 MAPK inhibitor SB 203580 has been reported both to abolish or to have no effect on protection. The aim was to investigate the role of p38 MAPK activation as trigger in the mechanism of ischemic preconditioning by using the p38 MAPK inhibitor, SB203580 and anisomycin (An)as activator of p38 MAPK.

Methods: Hearts were exposed to 25 min global ischemia. A 3X5 min cycle of ischaemia was used to elicit ischemic preconditioning. The p38 MAPK inhibitor, SB203580 (10μM), was used to bracket the ischemic preconditioning triggering phase. In separate experiments p38 MAPK was activated prior to ischemia by administration of anisomycin (An)(5 μM) for 3X5 min, 1X10 min, 1X10 min plus washout(W), and 1X20 min (without washout). p38 MAPK activation was determined by Western blot (dual phosphorylation antibodies). Protection was evaluated with functional recovery (aorta output) during reperfusion (Neely-Morgan isolated working rat heart model).

Results: Both ischemic preconditioning (3X5 min) and anisomycin (all modes of administration) significantly activated p38 MAPK. Ischemic preconditioning protected against ischemia (aorta output 16.6±1.8 ml/min vs. 3.8±1.5 ml/min in Non-PC hearts), whereas anisomycin (irrespective of protocol) failed to protect (An 3X5 min = 6.1±2.1, 1X10 min = 4.6±2.6, 1X10 min plus washout(W)= 5.3±2.8, and 1X20 min (with out washout)= 3.5±2.4. SB 203580 bracketing of the preconditioning protocol did not abolish the protective effect of preconditioning (recovery 26±0.9ml/min) but enhanced the protective effect of PC ($p<0.05$ for PC+SB vs. PC), and SB 203580 alone (3X5 min) did not have any effect on protection (aorta output 3.3±1.3 ml/min), excluding the possibility of a drug effect due to inadequate washout of drug prior to sustained ischemia.

Conclusions: Although p38 MAPK is activated during ischemic preconditioning, the protective effect of preconditioning is not dependent on activation of the stress-kinase. Inhibition of p38 MAPK during the preconditioning protocol enhances the protective effect of ischaemic preconditioning, indicating a detrimental role for p38 MAPK activation during the triggering phase.

1342 β-Adrenergic receptor stimulated preconditioning may protect against necrosis and apoptosis via inhibition of p38 MAP kinase

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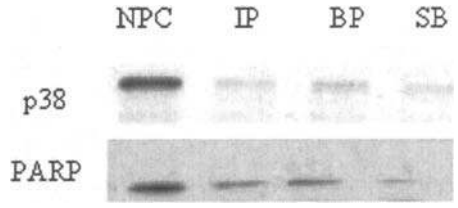
Background: The protective effect of ischaemic preconditioning (I-PC) in the rat heart is mediated by reduced activation of the stress-kinase p38 MAPK. Beta-PC (elicited by beta-adrenergic activation by isoproterenol administration) protects against ischaemia using functional recovery as end-point. The efficacy in reducing infarct size and apoptosis, and the mechanism of protection of beta-PC is unknown.
Aim: To (1) compare the effects of I-PC and beta-PC with regard to infarct size reduction and protection against apoptosis and (2) investigate the role of p38 MAPK in the mechanism of beta-PC.
Methods: Isolated perfused rat hearts were subjected to 25 minutes global ischaemia and 30 min reperfusion. Hearts were treated with I-PC (3 x 5 min ischaemia) and beta-PC (1 x 5 min 10-7 M isoproterenol) and the p38 MAPK inhibitor SB 203580 (10μM). Infarct size was determined with TTC staining, and apoptosis evaluated by determination of caspase-3 activation and PARP (Western blot). p38 MAPK activity was evaluated by Western blot (anti-dual phosphorylation antibodies).
Results: p-38 MAPK activity was equally reduced in hearts treated with I-PC, beta-PC and SB203580. This was accompanied by an equal decrease in Caspase-3 activation and PARP formation. Infarct size of hearts treated with I-PC, beta-PC and SB203580 was significantly reduced compared to non-PC hearts (24.1±2.27%, 22.53±3.3% and 23±1.8 vs. 42.5±2.3% ($p<0.05$).



P38MAPK and PARP in preconditioning.

Conclusion: I-PC and beta-PC both reduced infarct size and apoptosis, and was associated with reduced activation of p38 MAPK. The p38 MAPK inhibtor SB203580 reduced infarct size and apoptosis to the same extent. This may imply the stress kinase p38 MAPK as a mediator of protection against necrosis and apoptosis.

1343 C-Src/Bcl-xL pathway is involved in anti-apoptotic effect of endothelin-1 in H9c2 cardiomyocytes

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Apoptosis of cardiomyocytes is thought to be a feature of many pathological disorders, including congestive heart failure and ischemic heart disease. Since the loss of contractile cardiomyocytes due to apoptosis results in a furher decrease of cardiac function, the identification of the signaling pathway that mediate survival and/or apoptosis in cardiomyocytes is important. Recent investigations indicate that endothelin-1 (ET-1) plays an important role in congestive heart failure and ischemic heart disease. We therefore investigated the effect of ET-1 on cardiomyocyte apoptosis. The presence of apoptosis in rat H9c2 cardiaomyocytes was evaluated by morphological criteria, electrophoresis of DNA fragments, 4', 6'-diamidine-2'-phenylindole (DAPI) staining, and TUNEL analysis. ET-1 not angiotensinII prevented apoptosis induced by serum deprivation in a dose-dependent manner (1-100 nM). This anti-apoptotic effect of ET-1 was completely abolished by the treatment with selective ETA receptor antagonist BQ123, but not by ETB receptor antagonist BQ788. The use of specific pharmacologic inhibitors demonstrated that anti-apoptotic effect of ET-1 is mediated through a tyrosine kinase pathway (genistein and AG490) but not through PKC (calphostin C), MAP kinases (PD98059 and SB203580), or PKA (KT5270) pathways. Because c-Src family of tyrosine kinases has shown to be involved in apoptotic cell death, we next investigated the role of c-Src in the anti-apoptotic effect of ET-1. Western blotting using an antibody which recognizes the activated form of c-Src showed that activity of c-Src increased by 4.5-fold within 30 seconds in response to ET-1 stimulation. Adenoviral-mediated gene transfer of kinase inactive (KI) c-Src inhibited the anti-apoptotic effect of ET-1, whereas gene transfer of beta-galactosidase with Ad.LacZ had no effect. We further investigated whether Bcl-xL, an anti-apoptotic molecule, would be up-regulated by using a luciferase-based reporter system. ET-1 up-regulated Bcl-xL, and this up-regulation was inhibited by genistein or AG490 but not by calphostin C. The experiments using KI mutants for various tyrosine kinases revealed that c-Src (but not JAK1, Jak2, Syk, Tec, and Pyk2) is required for ET-1-induced up-regulation of Bcl-xL expression. These findings suggest that ET-1 prevents apoptosis in cardiac myocytes through the ETA receptor and the subsequent c-Src/Bcl-xL-dependent pathway, and provide a new insight into the molecular basis and therapeutic target for cardiovascular diseases including congestive heart failure and myocardial infarction.

1344 Induction of anti-apoptotic genes by ischaemic conditions

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In ischemic/reperfused myocardium nitric oxide and oxygen radicals are found increased. Both radicals induce apoptosis in normoxic cardiomyocytes. However, after simulated ischemia cardiomyocytes are transiently protected against apoptosis. To elucidate mechanisms involved in this mode of protection we now analyzed the expression of anti-apoptotic genes in cardiomyocytes exposed to ischemic conditions.
The NO-donor SNAP (100 μM) induced apoptosis in 13.2 ± 0.3% of cardiomyocytes determined by annexin/propidium iodide staining (vs. 4.0 ± 0.5% in controls, n=5, $p<0.05$). TUNEL-assay gave virtually the same results with 12.6 ± 4.9% TUNEL-positive cells vs. 5.4 ± 0.7% in controls (n=3, $p<0.05$). DNA-laddering could be detected after SNAP treatment. Release of cytochrome c from mitochondria into the cytosol increased by 103 ± 38% (n=5, $p<0.05$ vs. non-treated control) and the amount of the anti-apoptotic protein Bcl-2 associated with mitochondria decreased to 67.2 ± 13.9% within 6 h after SNAP-addition (n=8, $p<0.05$). The ability of SNAP to induce apoptosis after 3 h of simulated ischemia (anoxia in a glucose-free medium with a decreased pH) had vanished (4.6 ± 0.7% apoptotic cells). DNA-laddering was no longer found. Investigations on anti-apoptotic gene expression by RT-PCR revealed an upregulation of mcl-1 by 99 ± 62%, bcl-2 by 69 ± 26% and bcl-xl by 54 ± 26% (n=9, $p<0.05$). bcl-w expression did not change. The amount of Bcl-2 associated with mitochondria increased to 122.1 ± 6.7% (n=8, $p<0.05$ vs. normoxic controls). In the group of the IAP family (inhibitors of apoptosis), only IAP1-mRNA increased by 61 ± 32%. Survivin expression was slightly, but not significantly increased and mRNA's of XIAP and NAIP were not detected.
In conclusion, changes in cytochrome c and Bcl-2 location reveal involvement of mitochondria in NO-induced apoptosis in cardiomyocytes. Preceding ischemic conditions protect cardiomyocytes against this kind of apoptosis. The induction of anti-apoptotic genes of the bcl-2- and IAP-family under ischemic conditions may contribute to this mode of protection.

1345 The apoptosis regulator ARC prevents apoptotic and necrotic cell death in cardiomyocytes

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While apoptotic cell death of cardiomyocytes plays a role in ischemia-reperfusion, the predominant mode of cell death in myocardial infarction occurs via necrosis. Since the muscle-specific apoptosis regulator with CARD domain (ARC) was shown to prevent apoptotic cell death in the myogenic H9c2 cell line by targeting the mitochondrial apoptotic pathway we reasoned that protection from non-apoptotic cell death might occur by the same mechanism. Treatment of neonatal rat cardiomyocytes with 200μM H202 resulted predominantly in necrotic cell (>98%) death as determined by staining with ethidium-homodimer, absence of nuclear fragmentation as determined by staining with Hoechst 33342, absence of DNA-laddering and absence of immunofluorescence for cleaved caspase-3. In contrast, 24h of hypoxia resulted predominantly (>95%) in apoptotic cell death as determined by nuclear fragmentation and staining for cleaved caspase-3. Treatment with 200μM H202 caused necrotic cell death in 43.9±9.24% of cardiomyocytes after 1h and 73.7±18.23% after 12h. Infection with an ARC-adenovirus significantly reduced necrotic cell death to 26.1±21.4 after 1h and 24.98±12.1% after 12h (n=6), while neither treatment with the pan caspase-inhibitor ZVAD-fmk or an GFP-adenovirus were effective with respect to reduction of cell death. 24h of hypoxia significantly increased apoptotic cell death in comparison to control conditions (9.3±2.6 vs. 2.4±1.3, n=12). This apoptotic cell death was reduced to control-conditions by infection with an ARC-adenovirus or treatment with ZVAD-fmk but not by infection with a control virus. In the same set of experiments both hypoxia and treatment with H202 resulted in a breakdown of the mitochondrial membrane potential as determined by staining with mitotracker. Since this breakdown preceded both apoptotic and necrotic cell death we reasoned that ARC protected cardiomyocytes from both modes of cell death by preserving mitochondrial function. To directly address this question we pretreated cardiomyocytes with bongkrekic acid, an inhibitor of mitochondrial permeability transition. Bongkrekic acid prevented both apoptotic cell death in response to hypoxia and necrotic cell death in response to H202.
Conclusion: ARC protects cardiomyocytes from apoptotic and necrotic cell death by preserving mitochrondrial function. This defines ARC as a potentially important therapeutic target in the context of reperfusion injury and myocardial infarction.

CARDIAC ADAPTATION AND DYSFUNCTION IN HYPERTENSION: FROM MODELS TO PATIENTS

1346 Chronic sympathectomy improves survival and attenuates cardiac dysfunction and failure in rats with aortic banding-induced pressure-overload

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The chronic sympathetic overactivity that accompanies established heart failure (CHF) represents an inappropriate response that accelerates cardiac deterioration, and it has been unquestionably shown that CHF patients benefit from beta-blocker treatment. In the earlier stages of the syndrome, however, sympathetic activation may exert favourable effects, contributing to avoid cardiac failure despite increased load or reduced contractile mass. Indeed, limited and controversial evidence exists whether interfering with sympathetic activity before the onset of overt CHF has detrimental, neutral or beneficial effects. We therefore examined the course of experimental pressure overload hypertrophy (POH) in intact and chronically sympathectomized (Sx) rats. Treatment with 6-hydroxydopamine (150 mg.kg-1 twice a week) to produce chronic chemical Sx, or with vehicle (Veh) was administered to Sprague-Dawley rats previously subjected to aortic banding (B) or sham operation (S). After monitoring survival for 10 weeks, systolic pressure (SBP, carotid catheter) and left ventricular (LV) fractional shortening (%SF), end-diastolic (EDD) and end-systolic (ESD) dimensions (M-Mode echo) were measured. Lung, LV and right (RV) weights were indexed to body weight (wti, g/100 g). In the banded groups, survival was much worse in Veh- than in Sx-treated animals, with a 10-week mortality equalling 40% and 6%, respectively ($p<0.01$). There was no mortality in the sham groups. Further results are shown in the table (means±SD; *$p<0.05$ vs. corresponding S; #$p<0.05$ vs. corresponding Vh).

	EDD (mm)	ESD (mm)	%SF	SBP (mmHg)	LV wti	RV wti	Lung wti
S-Vh (n=8)	7.1+0.3	4.3+0.2	42+2	102+12	1.87+0.11	0.53+0.13	2.89+0.64
S-Sx (n=9)	7.2+0.3	4.4+0.2	39+2	96+15	2.08+0.21	0.58+0.05	3.64+0.42
B-Vh (n=9)	9.5+0.3*	6.3+0.3*	28+4*	154+19*	2.94+0.49*	0.76+0.30*	4.31+1.21*
B-Sx (n=14)	8.6+0.3*#	5.8+0.3*	35+2#	159+18*	2.48+0.59*#	0.61+0.13#	3.70+0.61

Thus in the course of experimental POH, chronic sympathectomy had clearly favourable effects on the degree of LV hypertrophy, chamber dilation, systolic dysfunction, lung congestion and RV involvement as well as, even more importantly, on mortality. Interfering with sympathetic activity during the developmental stage of an experimental model of POH leading to LV dysfunction and failure has markedly beneficial functional and survival effects.

1347 Inhibition of left ventricular hypertrophy prevents systolic dysfunction in mice with aortic banding-induced pressure overload

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Controversy exists whether the development of pressure overload-induced left ventricular hypertrophy (LVH) has beneficial, neutral or detrimental functional implications. Aim of this study was to assess the effects of preventing LVH by chronic propranolol treatment on LV systolic function and remodelling in mice with aortic banding.

Pressure overload was induced by thoracic aortic banding in 24 mice aged 3 months, 12 treated with propranolol (60 mg kg-1 d-1, Pro-Bd), 12 treated with vehicle only (Veh-Bd). Concurrent groups of sham operated mice (Sh) were studied (Pro-Sh, n=12; Veh-Sh, n=12). Four and 8 weeks after surgery, in vivo cardiac function, chamber size and LV mass (normalized to tibial length) were evaluated by cine magnetic resonance imaging (MRI) combined with intraventricular hemodynamic measurements obtained via a transcarotid, transducer-tipped catheter. LV mass figures provided by MRI strictly match with autoptic figures.

At the 4 week stage, carotid systolic pressure was similarly elevated in the two groups (Veh-Bd: 133±3 mmHg; Pro-Bd: 131±2 mmHg, p=ns), but normalized LV weight was 46% larger (145±4 mg vs 100±3 mg, $p<0.01$) in Veh-Bd compared to Pro-Bd mice, the latter being in this respect similar to the sham operated mice. Although not displaying LVH, Pro-Bd mice had significantly lower LV end-diastolic volume (61±4 ml vs 87±6 ml, $p<0.01$) and significantly higher LV ejection fraction (62±2% vs 41±2%, $p<0.01$) and LV +dp/dtmax (8454±125 mmHg.sec-1 vs 6137±135 mmHg.sec-1, $p<0.01$) compared to Veh-Bd mice. At the 8 week stage, LV weight was again larger in the Veh-Bd than in the Pro-Bd group, although in the latter LV dysfunction and remodeling started to develop. Histomorphometric analysis revealed that prevention of LVH in Pro-Bd mice pertained to the myocyte component whereas no protective effects were noted against LV fibrosis.

Thus in the pressure overloaded mouse in which the development of LVH is inhibited by propranolol administration, LV dimensions and systolic function are preserved, and LV systolic dysfunction is by no means facilitated and is rather markedly delayed. Taken together these findings indicate that i) LV hypertrophy represents a maladaptive mechanism which accelerates the progression to chamber systolic dysfunction and enlargement, and ii) the heart has the potential to cope with an increased mechanical load without increasing its contractile mass.

1348 The effect of dipping status on left atrial size in hypertension

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Background: It is known that left ventricular mass and left atrial size (LA) are both increased in hypertensive patients. LA enlargement is correlated with atrial fibrillation and cerebrovascular ischemic events.

It has been also shown, that non dipper hypertensive patients have increased cardiovascular risk compared to dippers. The dipping profile effect on LA dimensions has not been fully elucidated. The aim of this study was the investigation of the influence of dipping profile on LA size in hypertensive patients according to age.

Methods: The study comprised 4500 consecutive, untreated patients, (2440 men and 2060 women) with essential arterial hypertension. Twenty-four hours ambulatory blood pressure recordings were done in every patient. The patients were grouped as 2628 dippers (day systolic - night systolic mean arterial pressure>10mmHg) and 1872 non dippers. LA diameter and its indices, corrected for body surface area (LAI) or aortic root diameter (LA/AO) were calculated and the two groups (dippers and non dippers) were classified according to age decade

Results: LA increased ($p<0,0001$) with advancing age (r= 0.59) as did LAI (r=0.68) and LA/AO (r=0. 53) but had significantly higher values in non dippers (34.3 vs 32.7 mm $p<0.0001$).

The LAI had significantly higher values in non-dippers (18.4 vs 17.7 mm/m^2 $p<0.0001$), differentiating more in elderly patients (p=0.0008). Similar behavior was observed using the LA/AO ratio ($p<0.0001$).

LA correlated with daytime systolic blood pressure (r= 0.31) and pulse pressure (r= 0.37) and these relationships remained significant ($p<0.0001$) even after age correction (r=0.24 and 0.19 respectively)

Conclusion: LA enlargement is more severe in non-dipper hypertensive patients and the differentiation between dippers and non-dippers is age-related and more prominent in older patients

1349 Cardiovascular structure in patients with isolated office or ambulatory hypertension (The Vobarno study)

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Background and Objective: Cardiac alterations have been observed in subjects with isolated office hypertension (IOH) and in subjects with isolated ambulatory hypertension (IAH). Aim of this study was to evaluate both cardiac and carotid structural changes in a large sample of general population, according to the presence of office and ambulatory normotension (NT), hypertension (HT), IOH and IAH.

Patients and Methods: In 587 subjects (40-65 yrs) of the randomized sample of population participating into the Vobarno study, left ventricular mass index (LVMI), relative wall thickness (RWT), mean-maximum intima-media thickness (meanmaxIMT) were measured by ultrasound. Never treated subjects (n = 460) were divided in 4 groups according to blood pressure (BP) values measured in the clinic and during 24 hours monitoring: NT (office BP <140/90 and 24-hrs BP <125/80 mmHg), IOH (office BP >140/90 and 24-hrs BP <125/80 mmHg), HT (office BP >140/90 and 24-hrs BP >125/80 mmHg), and IAH (office BP <140/90 and 24-hrsBP >125/80 mmHg). Results are summarized in the table

	NT n 213	IOH n 98	HT n 96	IAH n 29
Sex (M) %	37	56	68	77
Age yrs	49 (8)	53 (8)*	52 (7) *	47 (9)
Smoke (y/n/ex)	60/29/11	59/18/23	52/28/20	61/19/20
O BP/24hrs BP	94(8)/86(5)	107(6)*/88(5)*	111(7)*/102(6)*	96(4)/98(4)*
LVMI g/h2.7	34(11)	41(11)*	44(13)*	38(12)*
RWT	0.32(0.06)	0.34(0.07)	0.35(0.06)*	0.36(0.07)*
IMT meanmax mm	0.84(0.18)	0.85(0.20)	0.93(0.26)*	0.92(0.17)*

* p at least < 0.05 vs NT

Subjects with HT, IOH, and IAH have greater LVMI in respect to NT, while RWT is higher in HT and IAH. Carotid IMT, controlled for age and gender, is greater in subjects with IAH than in NT. Prevalence of carotid plaque is greater in HT and IAH than in NT.

Conclusions: Structural changes in the heart and in carotid arteries may be observed in subjects with IAH, indicating that ambulatory BP measurement may help in identifying subjects with increased cardiovascular risk, that are not adequately picked up by office BP.

1350 Microalbuminuria accompanies left ventricular geometric adaptations in untreated essential hypeertensive subjects

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A slight elevated urinary albumin excretion (UAE) is well related with other target-organ damage. However the interaction between microalbuminuria (MA) and the spectrum of LV geometric pattern in essential hypertension has not been well defined.

Methods: For this purpose, MA was determined in 3 non-consecutive 24-h urine samples as UAE of 20-200mg/24h in a group of 249 untreated hypertensive subjects. Echocardiographic classification of patients into LV geometric patterns was based on relative wall thickness values and on gender specific values for LVMI.

Results: The group of patients with MA (n=119) was matched for age, sex, body mass index, smoking status and plasma cholesterol level with the group of patients without MA (n=130). Subjects with MA had significantly increased LVMI (111 vs 90 g/m^2, $p<0.0001$), relative wall thickness (0.46 vs 0.41, $p<0.001$) and office BP (161/101vs148/97 mmHg, $p<0.005$). For the pooled population, UAE was positively correlated to LVMI ($r=0.46$, $p<0.001$) and relative wall thickness ($r=0.47$, $p<0.001$). In the entire population, LV normal geometry (LV-NG), LV concentric remodeling (LV-CR), LV eccentric and concentric hypertrophy (LV-EH, LV-CH) was found in 34%, 33%, 12% and 21%, respectively. The incidence of LV-NG was significantly higher in normoalbuminuric compared to microalbumnuric subjects (55 vs 14%, $p<0.001$) while the incidence of LV-CH was significantly higher in microalbuminuric compared to normoalbuminuric subjects (32 vs 5%, $p<0.001$). Multiple regression analysis revealed that LV-CH was significantly associated with increased values of UAE and mean arterial pressure.

Conclusions: The higher prevalence of unfavorable LV geometric patterns in hypertensive subjects with MA compared to those without MA, may account for the worse cardiovascular outcomes associated with the presence of an increased UAE in hypertensive subjects.

1351 Left ventricular structure and function in sedentary and physically active subjects with left ventricular hypertrophy – The LIFE study

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Background: Exercise is known to lower blood pressure and to improve cardiac function in healthy and hypertensive subjects, but little is known of the relationship between exercise status and left ventricular structure and function in hypertensive subject with left ventricular (LV) hypertrophy.

Methods: A total of 958 hypertensive patients (41% women) aged 55-80 years (mean 66) with LV hypertrophy by either Cornell voltage-duration product or Sokolow-Lyon criteria on a screening ECG, were studied by echocardiography at enrolment in the Losartan Intervention For Endpoint Reduction (LIFE) trial. At baseline exercise status was obtained from a questionnaire and categorized into 3 groups as follows; Group 1 (sedentary): Never exercise; Group 2: <=30 min twice/week; Group 3 (physically active): >30 min twice/week.

Results: Exercise status did not differ in systolic, diastolic, pulse pressures, age or between genders. Sedentary (n=212) had, compared to physically active (n= 510), higher heart rate ($p<0.001$), weight ($p<0.001$), body surface area (BSA) ($p=0.02$), body mass index ($p<0.001$), LV mass (LVM) ($p=0.04$), LVM indexed for height or BSA ($p=0.004$), thicker interventricular septum ($p=0.012$) and posterior walls ($p=0.016$) and larger left atria ($p=0.006$). Variables of systolic endocardial as well as midwall LV function did not differ and only atrial filling fraction, among diastolic filling parameters, was significantly higher ($p=0.003$) in sedentary patients. There was no difference in relative wall thickness among the groups. Multiple regression analysis showed that higher LV mass was associated with sedentary lifestyle (beta=0.059, $p<0.05$) independent of body mass index (beta=0.256), male gender (beta=-0.445) and pulse pressure (beta=0.119, all $p<0.001$). Addition of age into the model (beta=0.097, $p=0.002$), render the effect of sedentary lifestyle exceeding the level of significance (beta=-0.053, $p= 0.067$). Furthermore heart rate did not enter the regression model.

Conclusions: Sedentary hypertensive patients with LV hypertrophy had compared to physically active patients, increased heart rate, larger left atria, thicker intraventricular septum and posterior wall. LV mass was higher in sedentary patients independent of gender, blood pressure or body mass index but not of age.

NEW FEATURES OF CORONARY BYPASS SURGERY

1356 Randomised trial of on-pump versus off-pump coronary artery surgery comparing clinical outcomes, graft patency and neuropsychological function

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Off-pump coronary artery bypass surgery (OPCAB) is widely believed to be associated with reduced mortality and post-operative morbidity. We conducted a study to compare graft patency, biochemical markers and neuropsychological function in patients undergoing OPCAB to those with cardiopulmonary bypass (CPB) in patients with three vessel disease.

Materials and Methods: 104 patients were recruited to a prospective, randomised study in a single institution. Exclusion criteria included single vessel disease, age > 80, recent infarct or CVA, ejection fraction <30%. One patient did not have surgery due to diagnosis of bronchogenic carcinoma. An identical standardised anaesthetic and surgical protocol was used for both groups. Patients were followed up at 3 months with quantitative coronary angiography to assess graft patency.

Results: 54 patients were randomised to OPCAB and 49 to CPB. Pre-op variables such as age (mean 63.4±8.3) and sex (85% male) were similar in both groups. The average number of grafts per patient was 3.4 in the CPB group, and 3.1 in the OPCAB group (p=0.02). 2 patients in the OPCAB group were converted to CPB intra-operatively. There were no in-hospital deaths or cerebrovascular accidents.

Post-operatively, in the OPCAB group, mean blood usage was 245 mls compared to 467mls in the CPB group (p=0.006). Times to extubation were similar in both groups, but length of post-operative stay was 7.3 days in the OPCAB group compared with 9.7 days in the CPB group (p=0.02). Adverse events at discharge were similar in both groups. Troponin T (TnT) and I (TnI), and creatinine kinase (CK-MB) levels were measured at 0, 6, 12, 24, 48 and 72hrs post-operatively. For TnT, the area under the curve was significantly higher in the CPB group, (p=0.005).

Preliminary analysis of data (n=71) at 3 months showed graft patency was 88.9% in the OPCAB group, and 95.1% in the CPB group (p=0.09). Adverse events at 3 months were similar in both groups. There were no deaths at 3 months in either group.

Conclusions: OPCAB appears to be safe and effective when compared to conventional coronary surgery. There was shorter length of stay, reduced transfusion requirement and decreased troponin release in the OPCAB group. Graft patency appears similar in both groups but larger studies will be required to determine the impact of OPCAB on long term outcomes.

1357 Coronary artery bypass grafting in multi-vessel disease on the beating heart: comparative study of 1200 patients

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Introduction: We present the mid-term results of coronary artery bypass grafting (CABG) for multi-vessel disease on the beating heart in comparison with the conventional surgery with the use of cardiopulmonary bypass.

Methods: We studied a total of 1200 patients undergoing isolated CABG by the same surgical team in a period of 24 months. During the first 10 months, all patients underwent operation with the use of cardiopulmonary by-pass and warm blood cardioplegia (Group A, n = 520), whereas during the next 14 months, all patients underwent CABG on the beating heart (Group B, n = 680). The following parameters were investigated: mortality, incidence of acute myocardial infarction (AMI), and stroke at day 30, intubation time, inotropic support, blood transfusions, serum kreatinine and duration of stay in Intensive Care Unit (ITU).

Results: The two groups were homogeneous with regard to clinical characteristics, such as age, sex, risk factors, angina class, ejection fraction and presence of peripheral vascular disease. Despite a trend in favour of group B, there was no statistical difference in total mortality and the incidence of AMI (2% vs. 0.4%, p=NS and 2.5% vs. 1.1%, p=NS respectively). There was significant reduction in the incidence of stroke in group B (3% vs. 0.6%, p<0.001),and less need for inotropic support and blood transfusions (62% vs. 17%, p<0.001 and 88% vs. 58%, p<0.01 respectively). Regarding the biochemical markers, serum kreatinine was less in Group B (0.9±0.3 vs. 1±0.4, p<0.009. The time spent in ITU was significantly less for the patients of Group B as compared to Group A(2.21±0.41 vs. 2±0.0, p<0.01).

Conclusions: Coronary artery bypass grafting on the beating heart is safer as compared to on- pump surgery. Off-pump surgery is associated with less post operative complications and quicker mobilization of patients as compared with conventional surgery. Long term results are awaited.

1358 Intraoperative angiography – A valuable method for quality control in off pump coronary artery surgery?

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Background: The information obtained by intraoperative graft angiography in off-pump coronary artery bypass grafting remains a matter of debate, despite the fact that anastomotic revision rates in the range of 10% after intraoperative graft angiography are reported in the literature. We present our initial experience with intraoperative angiographic evaluation of grafts placed on the beating heart.

Methods: A total of 29 coronary artery bypass grafts were investigated in 20 patients (17 female, 3 male, mean age 60). Transfemoral angiography was performed before (n=8) or after sternotomy closure (n=12) using an OEC 9800 mobile C-arm. Examination time was 24 (8-80) minutes, fluoroscopy time was 464 (211-1337) seconds. Mean contrast agent volume used was 150 (50-470) ml.

Results: No angiography-related complications occurred. Except for 3 aorto-coronary vein grafts, all bypass vessels could be visualized. Spasm of the graft or/and target vessels were present in 10 cases, 8 of them responded to intracoronary nitroglycerine application (0.25 mg). 2 grafts were severely stenosed requiring surgical revision. In addition, 2 proximal target vessel occlusions were observed and were left because of lacking evidence of intraoperative ischemia. There were no in-hospital mortality cases or perioperative ischemic events.

Conclusion: Our experience suggests that, despite being a time consuming examination technique, intraoperative angiography may reveal valuable information with possible demand for surgical revision.

1359 Coronary revascularization with free right internal thoracic artery: operative results in 1044 patients

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Objectives: This study evaluates the perioperative mortality and morbidity of patients having a free right internal thoracic artery (FRITA)-to-coronary artery graft as part of their coronary revascularization.

Methods: Between January 1992 and December 2001, 1,044 patients had a FRITA graft. Preoperative characteristics include mean age 52.8 ± 6.8 years; male sex, 1012 (96.9%); diabetes, 132 (12.6%); previous myocardial infarction, 579 (55.5%); three- vessel disease, 905 (86.7%); left main disease, 167 (16.0%); left ventricular ejection fraction < 40%, 113 (10.8%). In 3 patients (0.3%) the FRITA was the only arterial graft used, and in 1039 (99.5%) a pedicled left internal thoracic graft was also used. The mean number of grafts per patient was 3.1 ± 0.7 (2.0 internal thoracic grafts/patient), and endarterectomies were performed in 69 patients (6.6%). The FRITA was used to reach the circumflex marginal arteries in 866 patients (83.0%), the right coronary artery or its branches in 84 (8.0%), and diagonal or ramus intermedius in 92 (8.8%). The proximal anastomosis was constructed over a venous graft in 900 patients (86.2%) and directly into the aortic wall in the remainder. Cardiopulmonary bypass time was 77.6 ± 28.3 minutes.

Results: Perioperative mortality was 0.7% (7 patients). Only seventy three patients (7.0%) required inotropes, and 14(1.3%) intra-aortic counterpulsation and/or left ventricular assist device. The incidence of myocardial infarction was 4.3%. Thirty three patients (3.2%) had reintervention for hemorrhage and 42 (4.0%) for sternal complications. The incidences of respiratory failure, renal failure and cerebrovascular accident were 0.8%, 3.1% and 2.2%, respectively. The mean time of hospital stay was 8.4±8.7 days.

Conclusion: The use of the right internal thoracic artery as a free graft was associated with a low incidence of perioperative mortality and morbidity and allowed greater operative flexibility in arterial coronary revascularization.

1360 Coronary artery bypass graft using the left radial artery: early angiographic results

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Introduction: coronary artery bypass graft (cabg) surgery using the internal mammary artery (ima) in patients (pts) with obstructive coronary artery disease gives better long term permeability results than sapheinous vein grafts. Left radial artery (RA) can be used to perform such surgical coronary interventions.
Objectives: To evaluate the early post-operative permeability of cabg using RA.
Methods: All pts with recent surgical coronary revascularization using left RA were prospectively included and underwent selective femoral 4 French coronary grafts angiography before going out of hospital.
Results: From August 2000 to January 2002, 42 pts, (5 women, mean age 60.4 [42-78] had cabg using the left RA. Indications of revascularization were recent myocardial infarction in 6 pts, acute coronary syndrom in 11 pts (with 1 redux bypass), stable angina pectoris in 7 pts, silent ischaemia in 17 pts and valvular aortic stenosis in 1 pt. Risk factors were diabete mellitus in 15 pts, smoke in 26 pts, hypertension in 25 pts, and hypercholesterolemia in 27 pts.
Coronary status was 1 vessel disease (vd) in 2 pts, 2 vd in 5 pts, and 3 vd in 35 pts with 12 significant left main stenosis. 2 bypass grafts were performed in 22 pts, 3 grafts in 18 pts and 4 grafts in 4 pts. Left RA was used alone in 1 pt, with the left ima in 22 pts, with the 2 ima in 2 pts, with the left ima and 1 or 2 vein grafts in 16 pts, and with only 1 vein graft in 1 pt. Full revascularization was achieved in 22 pts (52%). Use of the RA concerned the left anterior descending artery in 1 pt, the first diagonal branch in 4 pts, the first or second left marginal branch in 29 pts, the right coronary artery in 8 pts. In 4 pts RA was used to revascularize 2 coronary arteries, (2 left coronary arteries in 2 pts, and 1 left and 1 right arteries in 2 pts). Local post cabg complications were radial nerve compression in 1 pt, and brachial hematoma in 1 pt. Pts didn't receive any specific antispastic treatment.
Selective RA grafts angiogramms were realized at the 13rd day [10-18]. Coronary RA bypass grafts were angiographically successfull without any abnormalities in 36 pts, (85.7%) and with focal non significant spasm or narrowing in 3 pts. There were 2 anastomotic stenosis (4.8%) between RA graft and the native coronary artery which needed RA angioplasty and stenting in 1 pt. RA graft was occluded in 1 pt, (2.4%).
Conclusion: In this prospective study cabg using RA appears to be a safe procedure with high early angiographic permeability success rate and no major local complications.

1361 Short-occlusive sutureless coronary anastomosis using adhesive

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Objective: We revisited a sutureless coronary anastomosis technique by means of a preglued side-to-side ITA-LAD kissing vessel wall apposition using octyl-cyanoacrylate, which, following the arteriotomy, was converted into an end-to-side anastomosis. The feasibility, patency and vascular wall healing of this facilitated coronary anastomosis technique was studied in porcine off-pump CABG.
Methods: In 8 pigs (80 kg), 8 low flow RITA-to-LAD anastomoses (pro-thrombotic condition) and 8 high flow control LITA-LAD anastomoses (less than 15 mL/min and about 50 mL/min, respectively) were evaluated intra-operatively and at 35 days. Anastomoses were examined by flow measurement, angiography and histology.
Results: All anastomoses (but one) were hemostatic after average construction time of 5.4 minutes and coronary occlusion of 1.6 minutes. One pig died at day 19 due to saddle type pulmonary embolism unrelated to graft failure. Fourteen anastomoses were fully patent at 35 days (FitzGibbon Grade A) with angiographic classical end-to-side anastomosis configuration. Histology showed mild repair intimal hyperplasia without aneurysm formation or medial necrosis.

Table: Intra- and postoperative measurements

	Anastomosis construction time (min)	Coronary occlusion time (min)	Hyperemic response index (peak/baseline flow)		Patency	Medial necrosis
			Intra-op	35 days		
Low flow (n=7)	5.2 ± 1.2	1.5 ± 0.3	5.2 ± 1.2	5.6 ± 1.8	7/7	0/7
High flow (n=7)	5.5 ± 1.1	1.7 ± 0.2	2.7 ± 0.6	4.2 ± 1.1	7/7	0/7

Data as mean ± SD

Conclusions: On the beating porcine heart, the sutureless-adhesive coronary anastomosis technique required an average 1.6 minutes coronary occlusion and revealed a favorable healing response, even in pro-thrombotic low bypass graft flow conditions.

VARIABLES INFLUENCING CORONARY FLOW: DO WE KNOW THEM ALL?

1362 Influencing parameters on flow velocity reserve in angiographical normal coronary arteries

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Background: Coronary flow velocity reserve (CFVR) is considered to be markedly influenced by clinical and hemodynamic parameters effecting the coronary microvascular resistance. The aim of the study was to determine variables influencing CFVR in angiographical normal arteries.
Methods: CFVR was assessed in an angiographical normal vessel in a total of 514 patients who were scheduled for PTCA of a single de novo lesion. Maximal hyperemia was induced using an i.c. bolus or i.v. infusion of adenosine. Continuous variables were dichotomized according to their mean value. Forward logistic regression analysis was performed to identify parameters that induce a low CFVR (below the mean value of 2.9; range 1.0-6.3). An independent t-test was performed for determination of clinical factors influencing predictors of CFVR.
Results: After univariate analysis of all relevant clinical and hemodynamic parameters, age >59, female gender, hypercholesterolemia, baseline APV >18 and heart rate >69 were identified as predictors of a low CFVR. Multivariate analysis revealed baseline APV >18 (odds ratio 1.9; 95% CI 1.3-2.9; p<0.01) and heart rate >69 (odds ratio 1.7; 95% CI 1.1-2.5; p=0.01) as independent predictors of low CFVR. Furthermore, diabetes (p=0.01) and hypertension (p<0.01) are positively associated with baseline APV. No clinical parameter influencing heart rate was identified.
Conclusions: Both baseline APV and heart rate are independent variables that influence CFVR. Baseline APV is positively associated with diabetes and hypertension. Although several other clinical and hemodynamic parameters were identified in a univariate way, they were no independent predictors of CFVR after multivariate analysis. Both baseline APV and heart rate should be taken into account in the interpretation of CFVR measurements for clinical decision-making.

1363 Likelihood of discordant results between fractional and coronary flow reserve: when should we measure the complementary haemodynamic parameter?

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Background: In 27% of the intermediate coronary lesions, we have observed discordant results between fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR), which may be caused by a number of underlying pathological conditions that would remain undetected if only coronary flow velocity or pressure was measured. Yet, the routine measurement of both intracoronary hemodynamic signals is not cost-effective in daily clinical practice.
Aim: To determine clinical, angiographic and intracoronary hemodynamic predictors of discordant results between FFR and CFVR when either intracoronary pressure or flow velocity was measured.
Methods: In 161 patients with 1- or 2-vessel disease (201 lesions, mean diameter stenosis of 56%) we observed 55 (27%) intermediate coronary lesions with discordant results between FFR and CFVR based on cut-off values of 0.75 and 2.0, respectively. Stepwise logistic regression analysis was performed using all clinical, hemodynamic, and angiographic data to assess the likelihood of a discordant outcome between the two flow reserve parameters, when either FFR or CFVR is known.
Results: Hypertension in combination with a heart rate >70 bpm was associated with FFR >=0.75 and CFVR <2.0 (odds ratio: 4.6, 95% CI: 1.6-13.1, p=0.004, n=22). A diameter stenosis >55% (odds ratio: 4.7, 95% CI: 1.6-13.9, p=0.005), a relative CFVR <0.90 (odds ratio: 3.6, 95% CI: 1.4-9.3, p=0.01) or a combination of both (odds ratio: 5.8, 95% CI: 2.3-14.6, p=0.0001) were associated with FFR <0.75 and CFVR >=2.0 (n=33).
Conclusion: If an intermediate coronary lesion with FFR >=0.75 is present in a patient with hypertension and a high heart rate, the likelihood that CFVR <2.0 for this lesion is significantly increased. For an intermediate lesion with CFVR >=2.0, the odds for FFR <0.75 are significantly higher when the stenosis is greater than 55% diameter reduction. The additional presence of a relative CFVR <0.90 further increases the likelihood for FFR <0.75. In order to rule out the presence of otherwise undiscovered coronary disorders such as microvascular disease, measurement of the complementary flow reserve parameter is advisable in these cases.

1364 A comparison of four intracoronary physiology indices of coronary microcirculation. Validation with histomorphometry in endomyocardial biopsies

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Background: Assessment of coronary microcirculation (MC) is hampered by the lack of a validated methodology. With this aim, we compared in heart transplant recipients the results of 4 intracoronary physiology indices of coronary MC status derived from intracoronary Doppler with or without concomitant measurement of pressure, with the actual structural changes in microcirculation documented in endomyocardial biopsies.
Methods: All patients (n=20) presented angiographically normal coronary arteries. Digital acquisition and storage of ECG, intracoronary Doppler flow velocity and pressure in the LAD was performed at baseline and during hyperemia (40 μgr adenosine ic) using a dedicated computerized system. Post-processing of data allowed calculation of 4 indices of MC status: coronary flow velocity reserve (CFVR), coronary resistance (CR), coronary resistance reserve (CRR), and slope of hiperemic diastolic pressure-flow relationship (DPFS). Endomyocardial biopsies were obtained simultaneously. Computerized morphometrical assessment of MC (% arteriolar obliteration and capillary density) was performed slides stained with monoclonal antibodies against endothelium. A bivariate regression analysis including both histological indices was performed with each physiological variable.
Results: A variable degree of MC disease was documented (arteriolar obliteration 75±7%, normal value 59±6%, p<0.0001; capillary density 637±216 mm^2, normal value 637±216, p=0.0001). Two physiological indices, DPFS (1.23±0.42 cm/s/mmHg) and CR (1.67±0.82 mmHg/cm/s) showed a good correlation with structural changes in MC (r=0.72, p=0.001 for DPFS; r=0.67, p=0.005 for CR). A significant, separate contribution of % arteriolar obliteration and capillary density for the values of DPFS and CR was found (beta coeff for %a arteriolar obliteration: DPFS –0.66, p=0.001; CR 0.44, p=0.02) (beta coeff for capillary density: DPFS 0.52, p=0.007; CR -0.65, p=0.002) On the contrary, neither CFR (2.06±0.59) nor CRR (2.41±0.81) showed an statistically significant relationship with structural changes of MC.
Conclusions: 1/ Significant differences were noted in the ability of 4 intracoronary physiology indices for detection of structural MC changes; 2/ absolute physiological measurements combining pressure and flow velocity (DPFS, CR) appear as the method of choice for this purpose; 3/ although a slight superiority of DPFS over CR was noted, the simplicity of the latter may justify its use for clinical or research purposes.

1365 Does alpha-blockade unmask residual myocardial resistance during adenosine in patients with coronary artery disease?

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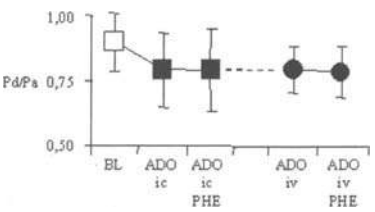
Adenosine (ADO), used for diagnostic purposes, is supposed to exhaust myocardial resistance. Yet, in patients (pts) with coronary artery disease (CAD), alpha vasomotor tone is enhanced and ADO might fail to reach minimal myocardial resistance.
Aim: To determine the presence of clinically relevant residual myocardial resistance after ADO administration.
Methods: Fractional flow reserve (FFR=hyperemic Pd/Pa, where Pa is mean aortic pressure and Pd mean distal coronary pressure) was assessed in 13 coronary stenoses (51±12%, diameter stenosis) of 13 pts, during IC bolus of ADO, before and 3 min after IC bolus of phentolamine (PHE, 12 μg/kg), an alpha 1-, alpha 2-adrenergic blocking agent. FFR was also measured in 10 coronary stenoses (46±10%, diameter stenosis) of 10 pts, during IV infusion of ADO, and during IV ADO plus PHE (given on top of maximal ADO hyperemia). All pts received an IC bolus of isosorbide dinitrate (ISDN, 3 mg) at the beginning of the protocols. All patients had normal left ventricular function.
Results: Since epicardial stenosis remained unchanged (ADO IC: before, MLD: 1,25±0,42; after, MLD: 1,33±0,39; n.s. - ADO IV: before, 1,48±0,22; after, MLD: 1,44±0,38, n.s.), changes in Pd/Pa ratio reflect changes in myocardial resistance. With IC ADO, FFR values were not different before and after PHE. During IV ADO, FFR remained constant before and after PHE (See graph). PHE administration did not induce any significant hemodynamic change in heart rate nor in blood pressure.
Conclusion: Myocardial resistance reached by IC and IV ADO cannot be further decreased by alpha-blockade.



1366 The effect of aortic valve replacement on coronary flow reserve in patients with significant aortic stenosis and normal coronary angiogram

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Background: Reduced coronary flow reserve (CFR) is an important cause of myocardial ischemia in patients (pts) with hemodynamically significant aortic stenosis (AOS) and normal coronary arteries. The aim of the present study was to examine the effect of aortic valve replacement (AVR) on left ventricular mass index (LVMI), CFR and clinical symptoms after a 1-year follow-up period in pts with significant AOS, normal coronary angiogram and normal resting left ventricular function.
Patients and methods: Sixteen patients (9 women and 7 men; mean age 66±7) were enrolled into the study. All patients underwent 2 months before and 1 year after the AVR a complete transthoracic echo study and CFR measurement by transesophageal echocardiography (TEE). Coronary flow velocity was obtained by pulse Doppler during TEE in the proximal left anterior descending artery. CFR was assessed with intravenous dipyridamole (0.56 mg/kg over 4 minutes) as a vasodilator agent. CFR was calculated as the ratio of the maximal averaged peak diastolic flow velocity (APV) to the resting APV.
Results are presented in the table.

	Before AVR	After AVR	p value
LVMI (g/m^2)	180.8±55.6	128.6±31.4	0.002
CFR	1.94±0.54	2.51±0.79	0.03
Peak AOS gradient (mm Hg)	94±25	25±8	0.001
Effort angina	7/16 (44%)	1/16 (6%)	0.01

Conclusion: In patients with aortic stenosis and normal coronary arteries, the symptomatic improvement 1 year after AVR is accompanied by the rise of CFR, possibly due to the reduction of LVMI.

1367 Additive effect of hypertension and diabetes on coronary flow reserve impairment

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Microangiopathy with impaired coronary flow velocity reserve (CFR) has been reported in patients with diabetes mellitus (DM) or essential hypertension (EH). It is unknown whether the combination of diabetes and hypertension may have an additive effect on CFR impairment. We measured CFR in 4 patient groups with normal left ventricular function and without significant coronary artery disease: Group 1 (n=28) were pts without DM and EH; Group 2 (n=12) were pts with DM without EH; Group 3 (n=11) were pts with EH without DM; Group 4 (n=13) were pts with DM and EH.
Average peak velocities (APV) were measured at baseline and after intracoronary administration of adenosine (12-18μg) using a Doppler-tipped flow wire. CFR was calculated by the ratio of baseline to hyperemic APV.
CFR was significantly lower in pts with DM and EH (2±0.5 in group 4 vs 2.9±0.7 in group 1, 2.5±0.4 in group 2 and 2.8±0.6 in group 3, p<.001). Similar results were found in patients with angiographic normal coronary arteries (CFR 2.3 in group 4 vs 4.1 in group 1, 2.5 in group 2 and 2.8 in group 3, $p < 0.02$) and in pts with unsignificant (<50%) coronary stenosis (CFR 1.8 in group 4 vs 2.8 in group 1, 2.6 in group 2 and 2.8 in group 3, $p < 0.002$)
Multivariate stepwise regression analysis revealed that combination of DM and EH ($p < 0.005$), left ventricular end diastolic pressure ($p < 0.004$) and heart rate ($p < 0.001$) were independently related to CFR.
Conclusions: Diabetics without hypertension have CFR similar to non-diabetics with hypertension. Diabetes and hypertension have an additive effect on impaired CFR.

RESTENOSIS RESEARCH: STILL WORTH THE EFFORT

1368 Expression of caveolin-1 in rabbit femoral and iliac arteries after balloon dilation

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Background: Caveolin-1 (cav-1) is the main protein component of caveolae. It has been found that cav-1 can play a role as a negative regulator in nitric oxide (NO) cellular signaling. Breakdown of collagen by matrix metalloproteases (MMP)is an essential feature in arterial remodeling. Since MMP 2 and 14 and cav-1 colocalized in caveolae, we hypothesized that cav-1 is involved in MMP activation.For this, we analyzed the localization and protein levels of cav-1 in iliac and femoral arteries at different time points after BD.
Methods: BD was performed in iliac and femoral arteries in New Zealand White rabbits (n=32). The animals were sacrified at different time points (2, 7, 14, 28 and 42 days)after BD. The contra-lateral arteries were used as a control. Expression and localization of cav-1 was performed using Western Blotting and immunohistochemistry. Arterial remodeling and intimal hyperplasia was measured by angiography and histology.
Results: Cav-1 was localized mainly in endothelial and smooth muscle cells. we determined the expression of cav-1(see table 1).The levels of cav-1 were upregulated after 14, 28 and 42days in BD arteries, but also in contralateral arteries at the same time points.Arterial remodeling and intimal hyperplasia also occurs after 7 days (see table).

	0days	2days	7days	14days	28days	42days
Iliac control	13,6± 3,3	19,4± 2,3	18,8±1,8	42,3±5,9*	47,9±3,9*	60,9±4,5*
Iliac BD	-	17,8± 4,1	18,8±4,9	33,4±7,6*	50,5±2,4*	74±5,4*
Fem control	21,6± 5,8	15,7±6,1	22,7±2,7	39,6±9,8*	61,8±6,9*	83,2±3,6*
Fem BD	-	19,4±3,3	17,7±3,1	31,7±3,5	55,3±4,6*	77,2±4,6*
DC (%)	0	3,8±2,4	-8,3±11,0	-9,0±4,6	-9,7±7,8	ND
IH(%)	0	0	1,5±0,6	5,0±1,3	16,7±2,7	ND

Cav-1 expression (OD*mm^2)(*=p<0.05 compared to 0 days)Fem=Femoral arteries;IH= Intimal hyperplasia fem+iliac); DC=Diameter change (remodeling,fem+iliac); ND= Not defined

Conclusions: Cav-1 expression is increased after BD and associated with remodeling and IH. Cav-1 expression is also increased in uninjured contralateral arteries. This finding suggest a systemic mechanism responsable for this up-regulation of cav-1 after balloon dilation.

1369 Time relation of the amount of macrophages in the plaque during the chronic phase of in-stent restenosis

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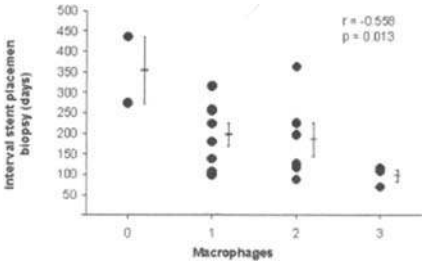
Background - Inflammation plays an important role in the acute phase of in-stent restenosis. But in the chronic phase, after approximately 30 days, the neointimal plaque consist mainly of vascular smooth muscle cells. In a previous study, we found that this neointima still contains small clusters of macrophages. In this study we investigated the relation between the amount of macrophages in the in-stent restenotic plaque and the time after the placement of the stent.
Methods - Biopsies from human coronary in-stent restenotic lesions were obtained with a pullback atherectomy catheter and immediately frozen in liquid nitrogen (n=19). The time between the placement of the stent and the biopsy varied from 69 till 465 days.
The biopsies were immunostained for smooth muscle cells, macrophages and ACE, and a semi-quantitative score was applied: 0 for no macrophages, 1 for a few or clusters of cells, 2 for <10% of cells positive, 3 for 10-50% of cells positive and 4 for >50% of the cells positive.
Results - As shown in the figure, an inverse correlation was found between the amount of macrophages and the time between the biopsy and the stent placement (p=0.013). The macrophages were mostly ACE-positive. Therefore, the amount of ACE also decreases during time (p= 0.011).



Amount of macrophages vs time-interval.

Conclusion - During the chronic phase of in-stent restenosis, the amount of macrophages in the neointima decreases, as well as the amount of ACE. This indicates that inflammatory cells play a role in the process of chronic in-stent restenosis, especially in the first phase.

1370 Inflammatory cells in post-balloon angioplasty restenosis and in-stent restenosis in relation to stable and unstable angina

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Objectives: To compare the tissue composition of restenotic lesion following balloon-angioplasty (BA) and stent-implantation and its relation to clinical expression of coronary syndromes.
Methods: A total of 32 patients with stable (SA) and unstable (UA) angina underwent directional coronary atherectomy for post-BA restenosis or in-stent restenosis. Cryostat sections of atherosclerotic plaques were immunohistochemically stained with monoclonal antibodies, alfa-actin (smooth muscle cells; SMC), CD-68 (macrophages; MAC) and CD-3 (T-lymphocytes; T-cells). The extent of SMC, MAC and T-cells were analyzed semi-quantitatively: 0=none, 1=few, 2=mild, 3=heavy staining.
Results: Morphologic analysis showed in 8 (out of 16) patients with in-stent restenosis T-cell clusters, that were not observed in patients with post-BA restenosis. In addition, there was a diffuse T-cell distribution in both restenotic lesions. The table shows the result of immunohistochemical staining of restenotic tissues in relation to the type of restenosis and the clinical manifestation of angina.

	SMC	MAC	T-cells
post-BA restenosis (n=16)	2.6 ± 0.1	1.6 ± 0.1	1.3 ± 0.1
in-stent restenosis (n=16)	3.0 ± 0 *	1.3 ± 0.1	2.0 ± 0 *
SA (n=16)	2.8 ± 0.1	1.3 ± 0.1	1.6 ± 0.1
UA (n=16)	2.8 ± 0.1	1.6 ± 0.1**	1.7 ± 0.1

Values are mean±SEM, *p<0.01 compared to post-BA restenosis, **p<0.05 compared to SA

Conclusions: In-stent restenotic lesions contain significantly more T-cells as compared to post-balloon angioplasty restenotic lesions. This could relate to an stent-induced T-cell mediated immunorespons. Moreover, the presence of macrophages in restenotic tissue is positively associated with the clinical expression of angina.

1371 The effect of modulating collagen turnover on in-stent restenosis: a study in the atherosclerotic and non-atherosclerotic Yucatan minipig

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Background: Collagen turnover is an important feature in restenosis following balloon angioplasty and stenting. Previously, we demonstrated that inhibition of matrix metalloproteinases (MMPs) by an oral MMP inhibitor significantly reduces late lumen loss (LLL) following balloon dilation by inhibition of constrictive remodeling. In the present study, the effect of the oral MMP inhibitor BB-2983 and an oral collagen synthesis inhibitor was tested on in-stent restenosis in the Yucatan minipig.
Methods: Seventeen non-atherosclerotic and 7 atherosclerotic Yucatan minipigs underwent bilateral stenting of femoral arteries with a balloon/artery ratio of approximately 1.2. Non-atherosclerotic animals either received MMP inhibition (MMPi, n=5 pigs), prolyl4-hydroxylase inhibition (P4Hi, n=6) or served as controls (n=6 pigs). Atherosclerotic animals either received MMP inhibition (n=3 pigs) or served as controls (n=4 pigs). Pigs were terminated at 42 days follow up. Angiography was performed at all time-points to determine LLL (defined as: lumen post intervention - lumen follow up). Stents were embedded in plastic and cut for cross-sectional area measurements. In each stent, neo intima formation (IH) was quantified in a proximal and distal segment, using Sis-analysis 2.1 software.
Results: See table.

In-stent restenosis

	Non-atherosclerotic			Atherosclerotic	
	control	MMPi	P4Hi	control	MMPi
LLL (mm)	0.5±0.1 (12)	0.2±0.0 (10)*	0.8±0.2 (10)	0.9±0.1 (7)	0.5±0.1 (5)***
IH prox stent (mm^2)	2.6±0.3 (12)	1.6±0.1 (10)*	3.6±0.3 (10)**	6.2±1.7 (6)	4.2±0.6 (5)
IH distal stent (mm^2)	2.5±0.2 (12)	1.5±0.2 (10)*	3.2±0.1 (10)***	5.4±1.2 (7)	2.7±0.4 (5)

values in mean ± sem, *p<0.007, **p=0.05, ***p=0.03, (n) = number of arteries

Conclusions: MMP inhibition by BB-2983 inhibited in-stent late lumen loss in the non-atherosclerotic pig. This effect was confirmed in the atherosclerotic pig. Prolyl4-hydroxylase inhibition did not reduce neo-intima formation and thereby late lumen loss following stenting.

1372 Seeding of intracoronary stents with AC133+ endothelial progenitor cells

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Background: It is well established that rapid regeneration of a functional endothelium after coronary stenting contributes to reduced restenosis and diminishes the risk for sub acute and late thromboses.
Therefore we tested if seeding of coronary stents with AC133+ endothelial progenitor cells in vitro leads towards a confluent endothelial monolayer on the stent surface.
Endothelial progenitors are known for their high regenerative potential which could contribute to rapid regeneration of a functional endothelium at the site of vessel injury in vivo.
We tested several stent materials and stent coatings in order to find out the best surface for progenitor cells to become adherent and grow to confluence.
Methods: AC133+ endothelial progenitors were isolated from granulocyte colony-stimulating factor - mobilized peripheral blood. Mononuclear cells were isolated by density gradient centrifugation over Ficoll-Hypaque, incubated with AC133 conjugated magnetic micro beads and processed through a magnetic separation column to obtain purified AC133+ cells. Isolated cells were expanded under defined culture conditions in IMDM supplemented with FCS, horse serum, SCGF and VEGF for 2 weeks.
Jostent® Flex stents, coated with heparin, aluminium oxide, ceramic, different extracellular matrix proteins, as well as uncoated 316L stainless steel were incubated with a suspension of progenitor cells for 2 further weeks. Cell coverage was evaluated by REM and confocal microscopy. Afterwards cells were recovered from stents by trypsin digestion, counted and analyzed for expression of several EC-markers by immuno-fluorescence staining. Further more we evaluated cell retention after balloon expansion and exposure of the stent to pulsatile flow for 1 hour.
Results: Within 2 weeks endothelial progenitor cells became adherent and grew to confluence on heparin-, aluminium oxide- and collagen-coated stents, whereas uncoated 316 L steel turned out to be no appropriate surface for cell attachment. Morphological features as well as the expression of versatile EC-markers revealed AC133-derived cells grown to confluence as endothelium. Expansion of stent and exposure to flow resulted in retention of cells up to 65%.

1373 REGENT 1 (Restenosis Gene Therapy trial): first clinical results after local intracoronary application of iNOS-lipoplex-gene product

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Neointimal hyperplasia causing recurrent stenosis and reocclusion is a major limitation of the clinical utility of percutaneous transluminal coronary interventions (PCI) and, more recently, stent placement. Experimental studies suggested that local intracoronary gene therapy could be an effective therapeutical tool to prevent restenosis after PTCA. In animals,neointimal proliferation after ballon injury has been shown to be effectively reduced after application of the inducible nitric-oxide synthase (iNOS) gene. The primary objective of this first multicenter, prospective, single-blind, dose escalation study was to obtain safety and tolerability information of the iNOS-lipoplex (CAR-MP583) gene therapy for reducing restenosis following PCI. Safety is measured as the combined clinical endpoint of Major Adverse Cardiac Events(MACE), defined as death, Q wave or non-Q wave MI, emergent bypass surgery, or repeat target lesion revascularization, 30 days after treatment with CAR-MP583. Local intramural CAR-MP583 delivery was achieved using a ballon infiltrator-catheter. Until now a total of 27 patients (pts) have been included in the study (6 pts. were treated with 0.5μg, 6 pts with 2.0μg, 6 pts with 5.0μg and 9 pts with 10μg).
Results: Application of CAR-MP583 was uncomplicated in 26 of 27 pts. The target vessels were the LAD (n=13), RCX (n=6) and the RCA (n=8). In one patient, periinterventional side branch occlusion with consecutive troponin elevation occurred. No MACE were observed during follow up controls after 7,30,60 and 90 days. 6-month clinical and angiographic restenoses rates will be available 9/2002.
Summary: Local intramural application of CAR-MP 583 for reduction of restenosis after PCI is feasible and save.

SUBCELLULAR REGULATION OF MYOCARDIAL CONTRACTILITY

1374 Alterations of cross-bridge kinetics in human failing myocardium

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In addition to the altered intracellular Ca^{2+}-homeostasis, changes in the recruitment of cross-bridges may result in myocardial failure, as well. Yet, evidence for alterations of isometric tension-dependent cross-bridge cycling in human myocardium is still missing. Therefore, we performed simultaneous measurements of the isometric Ca-dependent tension and actomyosin ATPase activity (MYO) in triton X-skinned fiber preparations of human non-failing (NF, n=9) and failing myocardium (dilative cardiomyopathy, DCM, n=11). The MYO/tension relation ('tension cost'), which resembles the cross-bridge detachment rate was analyzed as well.
In DCM, Ca-sensitivity of tension was significantly increased compared to NF ($EC50Ca^{2+}$: 1.39±0.14 vs. 2.22±0.41 μM). This was paralleled by a decrease in relative tension cost. Maximal Ca-activated tension (NF vs. DCM: 21.7±2.6 vs. 25.1±2.2 mN/mm^2), nHill (1.85±0.19 vs 1.87), Ca-activated MYO (+ 100±12 vs. +107±14 μM ADP/s) as well as the Ca-sensitivity of MYO ($EC50Ca^{2+}$: 1.39±0.32 vs. 1.06±0.11 μM ADP/s) were similar in both groups.
It is concluded that the increased Ca-sensitivity of tension in human failing myocardium may be attributed to an increased Ca-affinity of troponin C. This increase in the TNC/Ca-affinity may in turn induce a decline of the cross-bridge detachment rate. Although these alterations may contribute to the diastolic dysfunction observed in human heart failure, they may also represent a compensatory mechanism for the energetic situation of failing human myocardium.

1375 The essential role of mitochondrial ATP-sensitive potassium channel in cardiac inotropy

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This study investigates the role of mitochondrial ATP-sensitive potassium channel (mitoKATP) during the response to positive inotropic stress in Langendorff perfused rat hearts.
6 groups of 6 hearts were studied. The first 3 groups were initially perfused with modified Krebs-Heneseleit buffer containing 1.75 mM [CaCl2] and switched to a buffer containing 4 mM [CaCl2], 0,5 μM dobutamine, or 80 μM ouabain respectively. The last 3 groups were initially perfused with modified Krebs-Heneseleit buffer containing 1.75 mM [CaCl2] before inhibition of mitochondrial ATP-sensitive potassium channel by 5 hydroxydecanoate, a mitoKATP inhibitor. They were then switched to a buffer containing 4 mM [CaCl2], 0,5 μM dobutamine or 80 μM ouabain respectively, without 5 hydroxydecanoate. Two additional series of 6 hearts, challenged by high calcium in presence or absence of 5 hydroxydecanoate, were studied by 31P NMR spectroscopy. Inotropic challenged induced a 60 to 75% increase in rate pressure product. Perfusion of 5 hydroxydecanoate did not induce any change in left ventricular function in control conditions. However, it significantly decreased the stress-induced increase in rate pressure product to 15 to 45% ($p < 0.001$ vs without 5 hydroxydecanoate)and increased the rate of the initial stress-induced increase in ADP and decrease in phosphocreatine ($p < 0.005$ vs without 5 hydroxydecanoate).
This study provides for the first time a physiological role for mitoKATP. Opening of heart mitochondrial ATP-sensitive channel is essential for an adequate response to positive inotropic stress. We hypothesize that maintenance of mitochondrial volume during the stress requires the opening of mitoKATP and that the preservation of the architecture of the inter mitochondrial membrane space maintains the efficiency of energy transfer processes at the time they are most needed.Beside its role in cardioprotection against ischemia-reperfusion injury, mitoKATP could also be implicated in heart failure.

1376 Subcellular mechanisms of delayed stretch-induced inotropy in rabbit myocardium

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Mammalian myocardium is characterized by a biphasic inotropic response to stretch with an initial rapid, followed by a delayed increase in force. The first phase is believed to result from increased myofilament sensitivity to Ca^{2+}. In rat myocardium, the second phase was attributed to a stretch-dependent paracrine release of endothelin-1.

Methods: Rabbit right ventricular papillary muscles, electrical stimulation, isometric contractions (1 Hz; 37°C). Stretching to lmax, relaxing to 88%lmax for 30 min, again stretching to 98%lmax. Repetition of the same protocol with the same muscle after blocking the Na^+/H^+-exchanger NHE-1 (HOE 642 10μM; n=16), the Na^+/Ca^{2+}-exchanger NCX (KB-R7943 5μM; n=8), stretch activated channels, SAC (Gd2+ 10μM; n=11) or the ETA-receptors (BQ123 0.1μM; n=9). Action potential duration was recorded in 7 trabeculae at room temperature (floating electrode method).

Results: Stretching rabbit papillary muscles from 88% to 98%lmax resulted in a biphasic response. During the initial, rapid phase force increased by 144±9% ($p<0.05$). During phase 2, force increased further by 61±4%. Neither HOE642, KB-R7943, Gd2+ nor BQ123 pretreatment affected the force increase in phase 1. Inotropic response in phase 2 was unaffected by pretreatment with Gd2+ and BQ123. In contrast, HOE642 and KB-R7943 significantly blunted the inotropic response to stretch during phase 2 by 31±5% and 61±7%, respectively. (both $p<0.05$). Action potential duration was not significantly altered by stretch.

Conclusions: Rabbit myocardium is characterized by a biphasic inotropic response to stretch. The initial, larger phase is not dependent on recruitment of stretch-activated ion channels, ETA-receptor, NCX or NHE-1 activation. NHE-1 and NCX activation largely contribute to the inotropic response in phase 2, possibly via intracellular alkalinisation and $[Na^+]_i$ accumulation with "reverse mode" Na^+/Ca^{2+}-exchanger dependent Ca^{2+}-influx. APD-increase does not contribute to the NCX reverse-mode activation.

1377 Dose-dependent effect of SERCA1-expression in rabbit isolated ventricular cardiomyocytes

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Due to its kinetics, the SR-Calcium-ATPase of the fast-twitch skeletal muscle (SERCA1) is an interesting target for gene therapy of heart failure. We analysed the contractility of rabbit isolated ventricular cardiomyocytes after adenovirus-mediated gene transfer of the SERCA1-gene.

Isotonic shortening was measured in cells transfected at different multiplicity of infection (MOI) either with SERCA1-virus (Ad-SERCA1) or β-Galaktosidase (Ad-LacZ) as control.

Analysis of mRNA and protein expression levels exhibited an increase in transgene-expression which depends on viral concentration. In the functional measurements, the SERCA1-group showed a decrease in the time peak shortening (TTP) by 10.29% at MOI10 ($p<0.05$) and by 22.48% at MOI50 ($p<0.05$). The time from minimum cell length to 50%-relengthening (RT50) was reduced in SERCA1-group by 11.05% ($p=0.053$) at MOI10 and by 28.92% at MOI50 ($p<0.05$) (MOI10: n=11 isolations; MOI50: n=7 isolations). Fractional shortening was increased at MOI10 by 12.44% in the SERCA1-group compared with Ad-LacZ ($p<0.05$). At MOI50, however, we found a decrease by 21.85% in fractional shortening of Ad-SERCA1 ($p<0.05$).

These data show progressively faster twitch kinetics in relation to SERCA1 expression levels. At MOI10 we found a positive inotropic effect of SERCA1-expression, but we found a negative inotropic effect at MOI50.

The negative inotropic effect at high SERCA1 expression levels is most likely due to excessive activation of Calcium removal resulting in smaller Calcium transients. Therefore, dose of SERCA overexpression is critical for improvement of myocardial function.

1378 Depressed spark amplitude and decreased spark frequency in cardiomyocytes of transgenic mice with cardiac overexpression of Phospholamban

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Phospholamban (PLB), a phosphoprotein of the sarcoplasmatic reticulum (SR), regulates the Ca^{2+}-affinity of SERCA 2a. To investigate, the effects of different expression-levels of PLB on the Ca^{2+}-release from the SR and on the expression of other Ca^{2+}-handling proteins we measured: 1) whole-cell Ca^{2+}-transients (Fura-2 method) and resting Ca^{2+}-sparks in isolated cardiomyocytes of transgenic mice either 2-fold overexpressing (PLBOE) or lacking (PLBKO) phospholamban in comparison to their controls (CON) 2) the protein-levels of the ryanodine receptor type 2 (RYA2), triadin and FKBP12.6. in homogenates (Westernblots).

In cardiomyocytes from PLBKO, peak fura-2 ratio amplitudes were significantly increased (CON: 0.27±0.02, PLBKO: 0.36±0.03).This was accompanied by an elevated spark frequency [sparks/100μm*sec] (CON:1.51±0.08, PLBKO:4.59±0.18) and higher spark amplitudes (CON:1.54±0.01, PLBKO: 1.92±0.01). The protein expression of RYA2 (CON: 161.0±22.2 DU, PLBKO: 67.9±16.DU), triadin (CON: 265.3±30.0 DU, PLBKO: 72.8±13.6 DU) and FKBP12.6 (CON: 26.0±5.0 DU, PLBKO: 7.6±2.0 DU) was significantly decreased. Cardiomyocytes from PLBOE mice demonstrated significantly decreased Fura-2 ratio- (CON: 0.4±0.04, PLBOE:0.26±0.02) and Ca^{2+}-spark amplitudes (CON: 1.60±0.03),PLBOE: 1.37±0.01), as well as a lower spark frequency (CON: 1.78 ±0.13,??PLBOE: 1.33 ±0.11). The protein levels of the RYA2 (CON: 48.7±23.6 DU, PLBOE: 114.05±5.1 DU), triadin (CON: 57.4±20.3 DU, PLBOE: 170.9±6.2DU) and FKBP12.6 (CON: 5.7±4.0 DU, PLBOE: 11.7±3.0 DU) were significantly increased.

These data indicate that Ca^{2+}-release from SR correlates with the expression of phospholamban, despite adaptive alterations in the protein-levels of ryanodine receptor type 2 (RYA2), triadin and FKBP12.6.

1379 β3-Adrenoceptor mediated eNOS-activation reduces cardiac contractility by stimulation of the AKT-kinase

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The signal transduction pathway and the (patho)physiological implication of β3-adrenergic stimulation in human myocardium remains unclear. Therefore, we investigated isometric force of contraction (electrically stimulated, isometric contracting trabeculae), eNOS-activation (immunfluorescence studies) and Ser-1177 phosphorylation (western blot) as well as phosphorylation of the AKT-kinase (immunfluorescence studies, western blot) in human right atrial (RA, Bypass OP), left ventricular nonfailing (NF, donor hearts) and failing (DCM, dilated cardiomyopathy) myocardium after application of BRL 37344 (BRL), a preferential β3-agonist.

Application of BRL (10 μM) increased force of contraction in RA (+56%, n=8, $p<0.05$) and reduced contractility in left ventricular myocardium. The decrease in force of contraction was significantly increased in DCM (-27%, n=8, $p<0.05$) compared to NF (-9%, n=4). In RA, NF and DCM, BRL induced an activation of eNOS. To investigate whether this eNOS-activation is mediated by a stimulation of the phospholipase C/IP3/AKT-kinase signaltransduction pathway, the phosphorylation of AKT-kinase and eNOS (Ser 1177) was measured. Application of BRL (10 μM) resulted in a time-dependent phosphorylation of AKT kinase (max. 2 min.), which correlated with a Ser 1177-phosphorylation of eNOS.

Conclusions: 1) β3-adrenergic stimulation leads to a phosphorylation-dependent eNOS activation via the phospholipase C/IP3/AKT-kinase signal transduction pathway in human cardiomyocytes. 2) There are regional differences in the inotropic effects of β3-adrenergic stimulation in human myocardium. 3) The negative inotropic effect of β3-adrenergic stimulation is increased in human heart failure.

MOLECULAR MECHANISMS OF ATHEROSCLEROSIS FROM MOUSE TO MAN

1380 Reducing the gap junction protein connexin43 substantially protects against atherosclerosis in LDL receptor-knockout mice

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Intercellular channels present in gap junctions allow the direct exchange of ions and small metabolites between cells in contact thus coordinating physiological processes such as cell growth and differentiation. We have recently demonstrated increased expression of the gap junction protein connexin43 (Cx43) in specific subsets of cells in atherosclerotic lesions. Because the development of atherosclerosis critically depends on paracrine cell-to-cell interactions, we hypothesized that direct intercellular communication via gap junctions may be another key regulator of atherogenesis. Atherosclerosis-susceptible LDL receptor-deficient mice were intercrossed with mice heterozygous for a Cx43 null mutation (Cx43+/- mice). Male LDL receptor-deficient mice with normal (Cx43+/+LDLR-/-) or reduced (Cx43+/-LDLR-/-) levels of Cx43 of 8 weeks old (n=7 per group) were fed a cholesterol-rich diet (1.25%) for 14 weeks. Atherosclerotic lesions were measured by computer image analysis measuring the extent of sudanophilic lesions within the thoraco-abdominal aorta and aortic root. The composition of the atherosclerotic plaques was analyzed using immunostainings with cell specific antibodies. Increase in serum lipid profiles (total cholesterol, triglycerides) and body weight did not differ between both groups. We confirmed the reduced levels of Cx43 in Cx43+/-LDLR-/- mice by Western blots on total protein extracted from hearts. The progression of atherosclerosis was reduced by 50% in the thoraco-abdominal aorta of in Cx43+/-LDLR-/- mice; lipid deposition being for Cx43+/-LDLR-/- and Cx43+/+LDLR-/- mice 7.1±0.9% and 15.4±1.5%, respectively (mean±SEM, $p<0.05$). These results were confirmed in aortic root analysis. Interestingly, atheroma in Cx43+/-LDLR-/- mice contain less inflammatory cells and exhibit thicker fibrous caps with more collagen and smooth muscle cells, features associated, in human, with stable atherosclerotic lesions.
Taken together, these data indicate a critical role for Cx43-mediated gap junctional communication in atherogenesis, and may open up towards therapeutic strategies not only affecting paracrine cell-cell interactions but also gap junctional intercellular communication to reduce the evolution of this common disease.

1381 Intervention studies utilizing an apolipoprotein E knockout mouse model of plaque rupture

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The brachiocephalic artery of the apoE knockout mouse (apoE-/-) has been established as a site of predilection for plaque rupture. The aims of this study were twofold: 1) to test the hypothesis that the plasminogen activator system may be involved in the process of plaque destabilization and 2) to assess the plaque stabilizing effects of pravastatin. Double knockout mice, deficient in the genes for apoE and Plasminogen Activator Inhibitor-1 (apoE-/-:PAI-1-/-) were created. Eleven of these apoE-/-:PAI-1-/- mice and twelve apoE-/- controls were fed a high fat diet for 25 weeks. Serial sections were taken through the brachiocephalic artery and were examined for plaque ruptures. The thickness of the fibrous cap, the proportion of the plaque occupied by the lipid core, and the number of fibrous layers within the plaque were also determined. Additionally, 40 apoE-/- mice were given pravastatin 40 mg/kg/day in their drinking water whilst on the high fat diet. Controls comprised 60 apoE-/- mice drinking plain tap water. This study was planned to continue for 9 months, with assessment of the incidence of sudden death using survival curves, in addition to the histological examination as above. There were significantly more plaque ruptures in the apoE-/-:PAI-1-/- mice than in the apoE-/- controls (6 of 11 compared to 1 of 12, $p = 0.03$, Fisher's exact test). Furthermore, in those that had plaque ruptures, the lipid core occupied a significantly greater proportion of the plaque than in those without (44 ± 3% compared to 33 ± 3%, $p = 0.01$, unpaired t-test), and there were significantly more fibrous layers within the plaque (4.9 ± 0.3 compared to 3.4 ± 0.5, $p = 0.02$, unpaired t-test).
Preliminary results from the pravastatin study show a clear reduction in the incidence of sudden death in the treatment group (3 of 40 compared to 15 of 60, $p = 0.03$) at 4 months, however this study is ongoing and full results, including incidence of plaque rupture and plaque morphometery, are awaited.
These results suggest that the plasminogen activator system plays an important role in the process of plaque destabilization and rupture. They also demonstrate that this model has important correlates with human lesions, in that the proportion of the plaque occupied by lipid and the presence of previous healed ruptures both act as markers of instability. The preliminary data from the pravastatin study are encouraging, and the full results from this study will be very interesting, in that they may confirm that pravastatin does indeed reduce the incidence of plaque rupture and promote plaque stability.

1382 Adenovirus-mediated overexpression of tissue inhibitor of metalloproteinase-2 attenuates atherosclerosis in apolipoprotein E-deficient mice

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Atherosclerotic plaque rupture and subsequent occlusive thrombosis remain the underlying cause of sudden cardiac death. Matrix metalloproteinases (MMPs) and associated excessive matrix degradation is thought to mediate the progression of stable atherosclerotic lesions to an unstable phenotype prone to rupture. We hypothesised that overexpression of human tissue inhibitor of metalloproteinases-2 (TIMP-2), a natural inhibitor of MMPs, could inhibit atherosclerotic plaque development in atherosclerosis prone apolipoprotein E-deficient (ApoE-/-) mice, resulting in smaller more stable lesions.
Male ApoE-/- mice on a C57Bl/6 x Sv129 mixed background were fed a high-fat cholesterol-rich diet for 6 weeks to enable the onset of early atherosclerosis. All mice were then predosed via tail vein injection with empty virus RAd66 (1.5 x 10*9 pfu/mouse). After 4 hours mice were infected with either human RAd.TIMP-2 (0.2 x 10*9 pfu/mouse) or RAd66 (0.2 x 10*9 pfu/mouse) and returned to the high-fat diet. Serologic, histological and immunological analyses were carried out 4 weeks after adenoviral delivery.
Infection with RAd.TIMP-2 resulted in elevated plasma levels of TIMP-2 and resulted in a marked reduction (51%; $P=0.039$) in mean lesion area (0.66 ± 0.24 mm^2; $n=4$) as compared with RAd66 infected mice (1.34 ± 0.22 mm^2; $n=6$). Similarly, a significant reduction (45%; $P=0.034$) in lumenal occlusion was observed (25.20 ± 8.69%) compared to RAd66 mice (45.51 ± 5.43%). In addition, there was a marked loss in macrophage numbers, apoptotic cells as well as MMP proteins. Conversely, an increase in smooth muscle cells, collagen deposition and fibrous cap thickness was seen in RAd.TIMP-2 infected mice compared to controls. Finally, evidence of intra-plaque haemorrhage was observed in RAd.66 infected mice but was not apparent in RAd.TIMP-2 infected mice.
These findings indicate that elevated circulating levels of TIMP-2 attenuates the progression of early atherosclerotic lesions to more established or vulnerable lipid-rich plaques. Therefore adenovirus-mediated overexpression of human TIMP-2 in ApoE-/- mice demonstrates its role in promoting atherosclerotic plaque stability.

1383 Isolation and transduction of rabbit monocytes – Promising vehicles for local delivery of arteriogenic gene products

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Monocytes/macrophages (Mo) represent intriguing vehicles for genetherapeutic approaches to augment collateral growth (arteriogenesis) in ischemic diseases. After ex vivo transduction and re-injection they would home to sites of arteriogenesis and secrete a gene product of interest. An accepted model of arteriogenesis is the rabbit model of hind limb ischemia. However, isolation of rabbit monocytes is problematic and ex vivo transduction techniques have not been established. This study was designed to establish rabbit Mo isolation and to explore different methods of in vitro transduction. Rabbit blood (40 ml) was taken from the ear vein and a modified Ficoll-Paque centrifugation protocoll was elaborated. The leukocyte fraction was plated into culture wells containing macrophage medium. Adherent cells were cultivated for up to 7 days. We were able to isolate 530.000 cells/ml blood and FACS analysis confirmed a 90% purity of the Mo-culture. Following transduction techniques were systematically examined using a reporter gene coding for LacZ: adenovirus (av), liposomes (lp), and electroporation (ep). We determined both the transduction efficiency (TE) with in vitro X-Gal staining and quantified the activity of beta-galactosidase (gal) by spectrometry. As little as 25 plaque forming units (pfu) av resulted in a TE of 98±1% of Mo when infeced 24 h after isolation. gal activity rose from 3.2±0.1 (control) to 50.9±0.3 mU/Mio cells. av concentrations up to 250 pfu as well as GM-CSF activation (200 U/ml) of cultivated Mo for up to 7 days were not able to further increase gal activity (50.9±0.1 mU/Mio cells). Neither lp (different lipid formulations) nor EP were able to significantly transduce Mo despite systematic change of DNA/lipid ratio (lp), day of transduction (lp, ep), and voltage (ep). The homing of ex vivo av-LacZ-transduced Mo was impressively demonstrated by their intravenous injection into rabbits one day after femoral artery ligation and visualization in proximity to collateral vessels through X-Gal staining of histologic sections. We demonstrate that isolation of rabbit Mo is feasible but only viral transduction is effective. Their homing to sites of arteriogenesis has intriguing potential for genetherapeutic approaches.

1384 Introducing a new model for studying macrophage homing into atherosclerotic plaque in apoE-deficient mice

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Background: Previous work from our laboratory has shown that the influenza virus exerts prominent effects on the atherosclerotic plaques of apo E-deficient mice. Specifically, a marked increase in subendothelial inflammatory cells (macrophages and T-cells) and smooth muscle cells were noted and a case of plaque erosion with superimposed fibrin-rich thrombus was seen. Since cytokines could be a mechanism by which the virus exerts its effect on the plaque, we decided to test this hypothesis with administration of TNF-á and IL-1â. In order to visualize plaque homing of macrophages, and because we have experience with SPIO (superparamagnetic iron oxide) in MRI studies, we decided to combine the administration of cytokines with SPIO.
Methods: Eight apo E k/o retired breeders, approximately 11-month old were divided into 2 groups. Five received mouse recombinant TNF-á and IL-1â IP 0.2 ìg each; apo E k/o controls received 0.5 mL saline contaning 1% BSA. In addition, three wild-type, age matched mice received the same dose of cytokines. Three hours later, all animals were injected with I.V. SPIO (Feridex) (1mMol/kg of iron). Six days later, the recipients were euthanized and the aorta was perfused with PBS. The entire aorta was formalin-fixed and processed for light microscopy.
Results: In apoE k/o without cytokines little to no iron was deposited in the plaques. In apo E-k/o mice pre-treated with cytokines, prominent superficial mononuclear, iron-containing infiltrate was present. In multiple superficial areas, dense cell clustering was seen. Immunohistochemistry demonstrated that although most of the cells were iron-containing macrophages, some T-cells and smooth muscle cells were also present. Wild-type mice showed no iron uptake into their aortas.
Conclusion: Administration of a single dose of TNF-á and IL-1â induced a striking homing of macrophages and to a lesser extent of T lymphocytes and smooth muscle cells to the subedothelium of apo E k/o mice. This effect was not seen in age-matched apo E k/o mice not treated with cytokines and neither in wild-type mice. This study strongly suggests that, the influenza virus exerts its effects on the plaques (at least partially) through cytokine-mediated mechanisms. In addition, SPIO was shown to be a good marker for recent macrophage homing into the plaque.

1385 The cellular immune response to oxidized LDL aggravates atherosclerosis. Evidence from adoptive transfer studies in immunodeficient mice

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Atherosclerosis is associated with immune responses to oxidized low density lipoprotein (LDL) and certain microorganisms. The expression of HLA-DR by activated macrophages and activated T cells adjacent to these macrophages in the lesions strongly suggests that a cell mediated immune reaction is taking place in the process of atherosclerosis. However, the role of specific immune responses has remained unclear. We have previously shown that transfer of CD4+ T cells into immunodeficient SCID x apoE knockout (KO) mice accelerates disease (Zhou et al Circulation 2000, 102:2919). To further explore if this effect is dependent on specific disease-associated antigen, we have now transferred CD4+ T cells specific for oxLDL into SCID x apoE KO mice. As controls, we used CD4+ T cells specific for a non-relevant antigen (KLH) and naïve CD4+ T cells. After 12 weeks, all the mice that had received T cells had significantly aggravated lesion development. However, mice receiving CD4+ T cells specific for oxLDL had a substantially increased lesion progression compared to those receiving naive or KLH specific T cells. Circulating levels of the Th1 cytokine, interferon-gamma was increased in proportion to the acceleration of atherosclerosis. These data show, for the first time, that adoptive transfer of oxLDL antigen-specific T cells accelerates atherosclerosis. They support the notion that Th1 cellular immunity is proatherogenic and identify oxLDL as a culprit autoantigen.

PULMONARY VEINS IN ATRIAL FIBRILLATION: FROM ANATOMY TO ABLATION

1386 Three-dimensional intravascular ultrasound architecture of the pulmonary venous wall: implications for radiofrequency ablation

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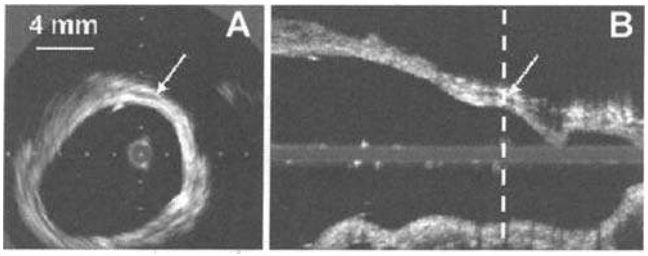
Recent basic and clinical electrophysiologic studies have documented the critical role of the wall of the pulmonary vein (PV) in the pathophysiology of paroxysmal atrial fibrillation.
Methods: Cross-sectional (figure A) and longitudinal (figure B) high-frequency (3.2F,30MHz) intravascular ultrasound (IVUS) images were examined in 32 PVs from 12 normal human autopsied hearts. The entire lengths of the PV from venoatrial junction to 2 cm distally were imaged using a motorized pullback at 0.5 mm/s to obtain a three-dimensional (3D) ultrasound reconstruction of each PV. Histological sections at the intervals allowed comparison to be made with ultrasound images.
Results: The cross-sectional ultrasound characteristic of the PV wall had a three-layerd pattern. The inner layer was an echogenic ring representing both endothelium and connective tissue of the media (mean thickness 1.4±0.2 mm). The middle layer was an hypoechogenic layer corresponding the sleeves of the left atrial myocardium surrounding the external aspect of the venous media (figure). This layer was thicker at the venoatrial junction (2.7±0.6 mm) and decreased toward the lung hilium. The outer layer was echodense, corresponding to fibro-fatty adventitial tissue (mean thickness 2.1±0.3 mm). A significant correlation ($p<0.001$) was found between longitudinal ultrasound and histological measurements of the myocardial content over the PV.



3D-ultrasound of the PV wall.

Conclusion: This study demonstrates the ability of 3D high-frequency IVUS to visualize the architecture and structure of the PV. Cross-sectional and longitudinal IVUS images can provide information on the thickness and distal limits of the myocardial sleeves and can be a valuable tool to help accurate targeting during ablation procedures.

1387 Three-dimensional intracardiac echocardiography (ICE) of pulmonary vein anatomy and location of circular mapping catheter in ablation of atrial fibrillation

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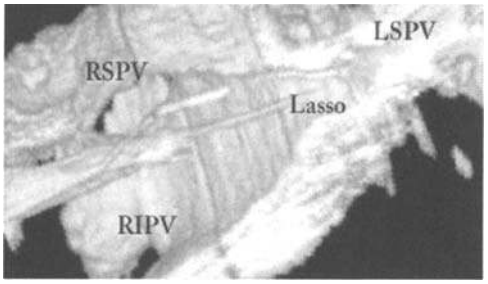
Background: The visualisation of pulmonary vein (PV) anatomy by angiography is limited, but crucial for identifying the ablation target for PV isolation. We investigated 3-D-ICE as an adjunctive imaging technique, to visualise PV anatomy and control positioning of circular mapping catheters (Lasso, Biosense Webster) in the PVs.
Methods: We performed 3-D ICE studies with a non-steerable 9 F-9 MHz ICE-catheter (Boston Scientific) with an ECG- and respiration triggered pull-back (TomTec workstation) starting 2-3 cm inside the PV pre and after PV isolation. PV ostium size, localisation and wall contact of Lasso (placed guided by fluoroscopy and electrical potentials) and lesion formation were studied.
Results: We report on 22 pull-backs in 5 pts (2f, 54±8 y) with an acquisition time of 318± 115 sec. 3-D reconstruction for left superior PV (LSPV) was possible in 5/5, left inferior (LIPV) in 4/5, right superior (RSPV) in 3/5 and right inferior (RIPV) in 0/5 cases. Averaged ostium size before ablation was (median/range) 14/12-18 mm (LSPV), 16,5/13-18 (LIPV), 21/19-22 (RSPV) in ICE compared to 14/12-18 (LSPV), 16,5/13-18 (LIPV) and 19/17-21 (RSPV) in angiography. First branching was visualised 13,6 ± 7,6 (2-22) mm distal of the PV-os. Position of Lasso was clearly identified in 11/12 veins with a distance of 9,3±4,2 (4-17) mm to the ostium. Post ablation thickening of the PV wall was detected in 6 PVs with no relevant stenosis. During the study 1 pt developed ST-elevation with no abnormality in coronary angiography suggesting ischemia due to air embolism.



Lasso in LSPV.

Conclusion: 3-D ICE of pulmonary veins provides detailed anatomical information of the proximal PV's and the position of circular mapping catheters. RF induced tissue changes in the PV wall can be visualised by ICE.

1388 Utility of intracardiac ultrasound imaging in guiding circumferential pulmonary vein ablation with the laser balloon catheter

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Background: Pulmonary vein (PV) isolation has been used as the endpoint for (AF) ablation in laser balloon ablation (LBA). Whether catheter tip-tissue contact is required in achieving successful electrical isolation of these veins has been unclear.
Method: To determine the role of intracardiac ultrasound (ICUS) in guiding PV ablation with LBA, and to assess the role of direct tissue contact, 59 PVs were ablated in 27 mongrel dogs. LBA was performed next to the PV orifice via a transseptal approach under fluoroscopic and ICUS guidance. Laser energy was delivered at 3.5 to 5.5 W/cm for 120 to 720 sec. Before laser application, ICUS color Doppler was used to assess for the presence of a blood flow leak between the targeted PV and the LBA catheter. After laser energy was delivered, PV isolation was established during normal sinus rhythm and distal coronary sinus and PV pacing with a 20-pole catheter positioned into the PV. Multivariate logistic regression analysis of the contribution of PV ablated, power delivered, time of application, presence of leak identified by ICUS, and balloon diameter and length to successful ablation isolation was undertaken.
Result: A total of 59 PV were ablated (23 RSPV, 27 LSPV, 8 LIPV, and 1 RIPV). Mean burn time was 279±177 sec, mean balloon diameter was 23±3 mm, and mean balloon length was 25±4 mm. Complete isolation was achieved in 38/59 (64%) PVs, and was significantly more common in the absence of blood flow leak: 30/38 (83%) versus 8/23 (35%) when a leak was documented ($p<0.05$, OR: 2.4, 95% CI: 1.4; 4.7). This was independent of time of application (302±223 sec vs. 266±148 sec, p=ns), power (3.5 W/cm, 4.5 W/cm, and 5.5 W/cm), PV ablated [8/23 (78%) RSPV, 18/27 (67%) LSPV, 2/8 (14%) LIPV, and 1/1 (100%) RIPV, $p<0.05$)], balloon diameter (24±3 mm vs. 22±3 mm, p=ns) and length (27±4 mm vs. 24±4mm, p=ns). The positive predictive value of leak was 65% and the negative predictive value was 83%.
Conclusion: An identifiable leak between PV and the LBA device seen by ICUS is predictive of lower PV isolation rates. ICUS may be useful for leak detection to avoid ineffective energy application during circumferential PV ablation.±

1389 Ostial pulmonary vein isolation in patients with atrial fibrillation utilizing a multipolar basket catheter and a new navigation system

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Atrial fibrillation (AF) is frequently induced by triggers originating from pulmonary veins (PV). Ostial PV isolation utilizing catheter ablation technique is a potential for cure. However, utilizing current ablation and mapping techniques a long procedure duration, prolonged fluoroscopy time and a high risk of recurrence are encountered.
Method: We studied 38 patients (mean age 52±12 years, 29 male) with refractory AF (paroxysmal n=29 persistent n=9). A 64-pole basket catheter (CONSTELLATION, EPT diameter=31 mm) was placed into the PV to identify the earliest PV activation during sinus rhythm (SR) or coronary sinus pacing. The ablation catheter was placed next to the electrodes showing earliest PV activation utilizing a novel navigation system (ASTRONOMER, EPT). The radiofrequency energy was delivered with a maximum temperature of 50° and a maximum power of 30 watt. Endpoint was complete elimination of all distal PV potentials during sinus rhythm.
Results: The mean number of procedures per patients were 1.4, mean procedure duration 238±94 minutes, mean fluoroscopy time 36±19 minutes. A total of 81 out of 84 mapped PVs were successfully isolated at the ostium utilizing a mean of 6.8 radiofrequency energy pulses. Complications: one pericardial tamponade, 10X carbonization observed on the splines/electrodes of the basket catheter (no clinical sequelae). The mean follow up is 8.4 ± 4.8 months and 32 out of 38 patients (84%) are were free of AF or had at least a significant improvement in symptoms.
Conclusion: The use of a multipolar basket catheter for mapping of the PV ostium facilitates identification of conduction paths from the left atrium into the PVs. The ASTRONOMER navigation system allows precise steering of the ablation catheter to areas identified as left atrial to PV conduction pathways.

1390 Pulmonary vein isolation by radiofrequency ablation using an irrigated multipolar ablation catheter in the ostium

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Background: Isolation of arrhythmogenic pulmonary veins (PV's) by radiofrequency current ablation (RF) has been introduced as a curative treatment of atrial fibrillation (AF). The use of conventional RF catheters is time consuming and carries the risk of thrombembolic complications. The aim of the present in vivo study was to evaluate a novel multipolar irrigated ablation catheter designed to create contiguous lesions encircling the PV ostium in a single ablation position. Methods: In 9 sheep, transseptal puncture and RF ablations were guided using intracardiac echo (ICE, Acuson, USA). The 6F RF catheter, formed with super-elastic helical elements with maximal radii of 9 or 10mm, was intended to position the distal portion of the helix within the PV. The proximal ablation section (tripolar, 22m coiled electrode length, Medtronic, MN, USA) at the PV ostium. A porous membrane covering the entire surface of the ablation electrodes achieved irrigation (10 ml/min, 0.9% saline). Additional to RF applications at the PV ostium RF was applied at both appendages and in the orifices of the coronary sinus (CS) and the vena cava (VC). Following RF ablation, the animals were sacrificed and macroscopical and histological analyses of the lesions were performed. Results: Positioning of the catheter could be achieved in 16 PV ostia. ICE showed an adequate wall contact of the RF electrodes. During 84 irrigated RF deliveries no impedance rise (>300 W) occurred and no coagulum formation at the electrode has been observed with the ICE. PV isolation or reduction of local electrograms (>50%) were observed following all RF applications in the PV ostia. A total of 28 lesions created in the PV, CS and VC ostia and atrial appendages showed no charring or crater formation at the endocardial surface. RF lesions were contiguous between 2 adjacent electrodes (depth 4 ±3 mm, width 5 ±3 mm).
Conclusions: Isolation of PV by the irrigated, helical RF is feasible without the risk of coagulum formation. Due to a single ablation position stabilized in the PV this RF catheter might simplify the procedure.

1391 Transcatheter cryothermal ablation for pulmonary veins isolation in patients with atrial fibrillation

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Cryothermal tissue injury is distinguished from hyperthermic lesions by the preservation of basic underlying tissue architecture and minimal thrombus formation. Such differences can be potentially significant in settings requiring extensive lesion formation, such as catheter-based procedure for the treatment of atrial fibrillation (AF). Safety and efficacy of cryoenergy were tested by attempting pulmonary veins (PV)isolation in 15 consecutive patients (pts)(13 males, mean age 57±8 years)with drug-refractory paroxysmal (12pts)/persistent (3pts)AF. Four pts had had prior right sided ablation and 3 prior conventional focal PVs RF ablation. A steerable 7F cryocatheter (Freezor, Cryocath)with 4 mm tip electrode using nitrous oxide as a refrigerant was used to produce cryolesions at the PVs ostia. Simultaneous circumferential PV activation obtained by a loop-shaped catheter guided cryothermal applications in each pt.Acute results are reported in Table 1. In the first two pts, conventional radiofrequency current was used after left upper (LUPV), right upper (RUPV)or left inferior (LIPV)PVs cryoisolation; in 2 pts RIPV was not targeted and in 2 pts RIPV isolation failed. Freezing resulted in painless ablation; no procedure relate complications occurred. At a mean follow up of 6±2 months, 10 pts (66%) were syptoms-free, 2 pts had chronic AF and 3 pts have sporadic AF episodes on drug. Conclusions: Cryoisolation of PVs is safe and may provide a potential alternative to radiofrequency current in clinical settings requiring extensive tissue destruction, such as the catheter-based approach for the treatment of AF.

MYOCARDIAL DISEASES

1392 Assessment of the significance of electrocardiogram abnormalities in junior elite athletes

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Background A significant proportion of athletes have Sokolow voltage criteria for LVH. A few have minor T wave inversion (TWI; < -0.2mV) in the inferior and right ventricular (RV) leads. The significance of these findings in unclear and poorly studied. The aims of this study were to correlate voltage criteria for LVH on ECG with LVH on echocardiography, and to evaluate the significance of minor T wave inversions in the inferior and RV leads.

Methods Between 1996 and 2001, 1350 junior (age 14-18) elite athletes and 200 healthy adolescent controls underwent ECG and echocardiography. Voltage criteria for LVH were correlated with LV wall thickness (LVWT) where LVH was defined as a LVWT > 2 SD of the predicted mean derived from the controls. In patients with TWI we looked for cardiomyopathy and anomalous coronary arteries on echocardiography.

Results Sokolow criteria for LVH were present in 45% of athletes and 23% of controls. On echocardiography, LVH was seen in 63 (12%) athletes but in no controls. The Sokolow criteria for LVH were positive in all individuals with LVH at echo (sensitivity = 100%) but with a high false positive rate (33% in athletes and 25% in controls; specificity = 67%). In contrast, the Romhilt-Estes criteria for LVH were specific (100%) and sensitive (92%).

Inferior TWI was seen in 0.6% of athletes but no controls. It was also present in RV leads in 20 athletes and 3 controls. TWI was absent in other territories. Echo was normal in these subjects and no anomalous coronary arteries were identified.

No athlete with LVH had q waves, LBBB, ST depression, deep T wave inversion. Also, no athlete with RV TWI exhibited epsilon waves or RV ectopics.

Conclusion Sokolow voltage criteria are a common finding in junior elite athletes. They are a sensitive, but non-specific marker for LVH. The Romhilt-Estes criteria offer a more specific, and thus better marker for true LVH. Furthermore, junior athletes with true LVH don't have additional ECG changes seen in cases of pathological LVH such as HCM. The presence of these changes should deter a diagnosis of athlete's heart.

Minor TWI in the inferior and RV leads is seen in a minority of junior elite athletes. These ECG changes were isolated and not accompanied by other findings indicative of a cardiomyopathic process. They most likely represent part of the normal paediatric ECG.

1393 Cardiac condition in myotonic dystrophy

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Myotonic dystrophy (MD) is a common form of adult muscular dystrophy frequently associated with cardiac complications. However the cardiac condition of these patients is always unclear as is the incidence of cardiac events.

Since 1994 we, consecutively, enrolled 55 patients with MD diagnosis on the basis of electromyography and molecular genetic. Each patients underwent physical examination, ECG, 24 hours ambulatory ECG, electrophysiological study and determination of systolic and diastolic function of left ventricle (LV) by radionuclear angiography. All patients were consulted once a year.

At time of enrollement, no patient had heart failure; abnormalities of atrioventricular (AV) conduction were present in 58% of patients and 50% of patients had a lengthening of HV interval during electrophysiological study justifying implantation of a prophylactic pace maker. Atrial arrhythmias were recorded in 8 patients. LV diastolic function was altered in 72% of patients with minor alteration of LVEF in only 16% of patients.

During the follow up (40.5 * 30 months), 24 pts (43%) developed 36 cardiac events: one sudden death, 15 complete AV block, 15 sustained atrial arrhythmias, and 5 non sustained ventricular tachycardia. No patients developed heart failure. Three patients died of respiratory insufficiency. Complete AV block occurred only in the group of patients with lengthening of HV interval at baseline evaluation.

In MD cardiac abnormalities are frequent especially in term of AV conduction, atrial and ventricular arrhythmias. Whereas LV diastolic dysfunction is frequent, patients rarely developed clinical heart failure. That cardiac condition justifies a regular cardiac control and implantation of prophylactic pacemeker in patients with lengthening of HV interval.

1394 Characteristic yearly progression of electrocardiographic abnormalities in cardiac Fabry disease

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Background: We reported that we had detected cardiac Fabry disease, an atypical variant of Fabry disease with manifestations limited to the heart, in 3% of unselected male patients with left ventricular hypertrophy (LVH) of unknown cause. Since Fabry disease results from a deficiency of alpha-galactosidase A (alpha-gal A) and enzyme replacement is now a treatment option for the disease, we sought to establish cardiac parameters over time to evaluate the effect of therapy. We report here the first characteristic serial electrocardiographic changes in patients with cardiac Fabry disease. Methods: The diagnostic criteria for cardiac Fabry disease included the presence of LVH, low plasma alpha-gal A activity, and the absence of other typical symptoms of Fabry disease such as angiokeratoma, acroparesthesias, hypohidrosis, and corneal opacities. We performed serial electrocardiograms (ECGs) in 10 consecutive male patients with cardiac Fabry disease over periods ranging from 3 to 14 years (mean, 7.4±4.0), assessing rhythm, PR interval, QRS width, and QRS voltage. Arryhthmias were evaluated by 24-hour Holter monitoring. Results: The first ECGs were obtained at 60±8 years of age and the latest at 68±8 years. In the first ECGs, one patient had a first degree atrioventricular (AV) block. Over 3 years his PR interval elongated significantly. The remaining 9 patients showed normal sinus rhythms initially. Among these 9 patients, one developed a complete AV block and 4 developed first degree AV blocks over time. Mean PR intervals from 9 patients with sinus rhythms increased from 0.19±0.03 to 0.22±0.04 seconds ($p<0.05$). Intraventricular conduction delays, present in 6 patients on the first ECGs, were present in 9 patients on the latest ECGs. Mean QRS width from all 10 patients increased from 0.13±0.04 to 0.17±0.04 seconds ($p<0.01$). In the initial ECGs, 8 patients had left ventricular (LV) high voltage. However, none of the patients had LV high voltage on the latest ECGs, even though all still had LVH on echocardiogram. By Holter monitoring, ventricular premature contractions (VPCs) were detected in all 10 patients. In 7 patients evaluated with serial Holter monitoring, ventricular tachycardia appeared. Conclusion: In patients with cardiac Fabry disease, conduction delays and VPCs worsened and LV high voltage attenuated despite the presence of LVH with the duration of the disease process.

1395 Left ventricular hypertrabeculation/noncompaction in 62 patients: Prevalence and association with other cardiac and neuromuscular disorders

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Background and Objectives: Few data are available about the prevalence of left ventricular hypertrabeculation/noncompaction (LVHT), the number of investigations necessary to diagnose LVHT and the rate of associated cardiac and neuromuscular disorders (NMD). Aim of the study was thus to assess 1. the prevalence of LVHT, 2. the number of echocardiographic examinations necessary to diagnose LVHT, 3. cardiac abnormalities are associated with LVHT and 4. the rate of NMD in patients with LVHT.
Methods: LVHT was diagnosed if in one plane >3 trabeculations apically to the papillary muscles were seen and Doppler imaging visualized intertrabecular spaces perfused from the ventricular cavity. All patients in whom LVHT was diagnosed between June 1995 to December 2001 underwent a clinical cardiological examination. It was noted, after how many examinations LVHT was diagnosed. All LVHT-patients were invited for a neurological examination.
Results: LVHT was diagnosed in 62 (12 female) patients with a mean age of 50 (18-75) years. The prevalence of LVHT was 0.24%/year. In 47% of the patients LVHT was diagnosed at the first echocardiographic examination, in 25% more than 3 examinations were necessary. In 97% of the patients LVHT was associated with echocardiographic abnormalities, ECG abnormalities in 92%, cardiac symptoms in 89%, heart failure in 73% and arrhythmias in 65%. Among the 49 LVHT-patients who underwent a neurologic examination, 82% had a NMD and 18% were neurologically normal.
Conclusions: LVHT is a heterogeneous echocardiographic finding which is often overlooked, more prevalent than previously believed and associated with NMD in the majority of patients.

1396 Impact of disease activity on left ventricular performance in patients with acromegaly

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Background: In patients with acromegaly, abnormalities of systolic and diastolic left ventricular (LV) performance, mostly associated with hypertension and/or LV hypertrophy, have been reported. We used two-dimensional/Doppler echo methods and tissue Doppler imaging (TDI) to elucidate the impact of disease activity on LV function in patients with acromegaly.
Patients & Methods: In a prospective study design, echocardiographic measurements were performed in 15 patients with active acromegaly (mean age-adjusted serum insuline-like growth factor-I (IGF-I) level 420± 170 ng/ml, mean growth hormone (GH) nadir during a 75-g oral glucose load 12.3± 30.1 μg/L, AA group), in 18 patients with cured (mean IGF-I level 205± 115 ng/ml, mean GH nadir during glucose load 0.72± 0.34 μg/L, n=14) or well controlled acromegaly ((normal age-adjusted ranges of IGF-1 levels under medication with somatostatin analogues: 354± 88 ng/ml, n=4), CA group) and in 24 control subjects (CON group). Acromegalic subjects with systemic hypertension, diabetes mellitus, coronary artery disease or valvular lesions were excluded. All study subjects underwent conventional 2-D/Doppler echo measurements including mitral and pulmonary venous flow velocities and assessment of ejection fraction (EF) and 'Tei-Index' (isovolumic contraction time and isovolumic relaxation time divided by ejection time). Systolic and diastolic mitral annular velocities (S', E', A', E'/A'-ratio) were derived from pulsed TDI.
Results:

Group	EF (%)	mitral E/A-Ratio	S'	E'	A'	E'/A'-Ratio	Tei-Index
CON	60±9	1.12±0.33	8.3±1.3	10.0±1.7	10.0±1.7	0.98±0.16	0.40±0.06
AA	58±9	0.78±0.22*	7.8±1.7	6.8±1.7*	10.3±1.8	0.68±0.22**	0.54±0.13**
CA	58±9	1.11±0.36	8.2±1.5	9.1±3.0	11.1±2.7	0.90±0.32	0.44±0.07

* p<0.05, ** p<0.01 AA vs. CON/CA

Conclusion: Disease activity has a significant impact on LV performance in patients with acromegaly. In subjects with active disease, diastolic dysfunction and beginning impairment of 'overall' LV performance are present. TDI analysis of mitral annulus velocity and assessment of the Tei-Index complement the evaluation of LV performance and might be a useful addition in the diagnostic work-up of acromegalic patients.

1397 Cardiac amyloidosis: electron and immuno-electron microscopy of abdominal fat allows identification and characterization of amyloid fibrils

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The diagnosis of cardiac amyloidosis, suspected on the basis of clinical and echocardiographic findings, is usually made by means of endomyocardial biopsy (BEM).
Given that fat tissue is a favorite site of fibril deposition in several systemic amyloidoses, we tested that hypothesis that patients presenting with the clinical phenotype of restrictive cardiomyopathy suspected to be due to myocardial deposits of amyloid also have fat tissue deposits. To this aim, we evaluated the role of electron microscopy and immuno-electron microscopy studies on abdominal fat fine-needle biopsy samples in diagnosis and characterization of cardiac amyloidosis. We investigated 17 patients with restrictive cardiomyopathy suspected to be due to amyloidosis. Patients underwent physical examination, electrocardiography, 2-D and Doppler ecocardiography, immunofixation of serum and urine to detect monoclonal immunoglobulins and abdominal fat (AF) biopsy. Of the 17 patients, 15 had a corresponding myocardial tissue study, either endomyocardial biopsy or autopsy study. AF was investigated with polarized light (Congo red), electron and immuno-electron microscopy using specific antibodies to kappa and lambda light chains, apolipoprotein A1, serum amyloid A (SAA) and transthyretin (TTR). The ultrastructural study of fat tissue samples identified amyloid deposits in 17/17 cases, and in the corresponding myocardial tisuue in 15/15 cases. Immuno-electron microscopy specifically stained amyloid fibrils with antibodies anti-lambda (n = 9), -kappa (n = 2), -apolipoprotein A1 (n = 2) and -TTR (n = 4). Immuno-electron microscopy revealed TTR immuno-labelling in 3 patients with accidental monoclonal components. TTR and apolipoprotein A1 positive cases carried missense mutations in the corrisponding genes. Our results demonstrate that amyloid deposits are present in the abdominal fat of patients suspected to have cardiac amyloidosis and that immuno-electron microscopy characterizes amyloid protein in all cases.

PSYCHOSOCIAL CONSEQUENCES OF CARDIOVASCULAR DISEASE

1398 Quality of life in patients with symptomatic multivessel coronary disease

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Background: although coronary angioplasty (PTCA) and coronary bypass surgery (CABG) are routinely used, there is no conclusive evidence that these interventional methods offer greater benefit than medical therapy (MT) alone as far as quality of life (QOL).
Objective: This study sought to evaluate the QOL of three possible therapeutic strategies for patients with symptomatic multivessel coronary disease and preserved ventricular function.
Methods: a total of 7783 elegible patients with multivessel disease were screened in a single institution and 611 7.8% patients were randomly assigned to undergo CABG, 203 to PTCA 205 and 203 to MT. QOL was evaluated by SF-36 questionnaire by interviews, in the pre treatment phase and 6 and 12 months of follow up.
Results: although all treatments offered improvement in QOL, such amelioration was greater in surgical group (table, *p<.0001).

Quality of life first year MASSII

Treatment	ptca		medical		cabg	
period	pre	12m	pre	12m	pre	12m
physical functioning	59.2	72.8*	50.2	66.2*	46.6	73.5*
role physical	34	52.6*	23.4	39.8*	20.7	48.2*
general health	64.5	63.8	63.4	60.8	62.5	64.4*
mental health	65.9	74.6*	63.4	70.4*	64.4	74*
vitality	64	72.2*	55.6	61.6*	56.1	73.8*
role emotional	51.9	67.1*	49.8	64.9*	45.5	68.9*
social functioning	57.5	70*	57.4	62.7*	52.7	66.9*
bodly pain	63.1	75.4*	61.7	70.1*	56.8	76.8*

*p <.0001

Conclusion: In conclusion surgical treatment offers better QOL among patients with extensive CAD than PCTA or MT.

1399 Quality of life and coping strategies in patients undergoing coronary angioplasty

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Background: In patients (pts) with coronary artery disease (CAD) both a reduced quality of life (QOL) and pathologic coping strategies (Cop) are described. There is, however, a lack of systematic studies comparing QOL and Cop in stable vs. unstable angina.
Methods and Results: This pilot study assessed QOL and Cop in 60 patients (mean age 60±11 years, 47 male) undergoing coronary angioplasty (Group I: urgent, n=30, Group II: scheduled, n=30). There were no significant differences in pts clinical characteristics with respect to age, gender, extend of CAD, and concomitant disease between the two groups. Patients completed the Seattle Angina Questionnaire (SAQ), the Medical Outcomes Study Short-Form Survey (SF-36) and the Trierer Coping Scales (TSK) in order to determine QOL and Cop, respectively. All but the SAQ treatment satisfaction (Sat) subscale were similar between groups. Sat was higher in Group I (89±12 vs. 79±16, p=.013 vs. Group II) with higher values indicating more Sat. Among the Cop scales Group I pts exhibited more rumination (Rum, 46±11 vs. 52±8, p=.05 vs. Group II) with higher values indicating pathologic tendencies. All other Cop subscales were similar between groups. Mental health was reduced in Group II (72±16 vs. 63±17, p=.041 vs. Group I) with both Sat (Beta=0.364, p=.041) and Rum (Beta=-0.246, p=.046) being independent predictors.
Conclusion: Early angioplasty may improve patients treatment satisfaction and prevent pathologic coping strategies.

1400 Hormone replacement therapy, ethnicity and psychological health in women: results from the NHLBI-sponsored WISE study

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Background: Prior observational studies demonstrate that white compared to black women are more likely to use hormone replacement therapy (HRT). Little information exists regarding use and psychological factors associated with HRT use among black women.
Methods: WISE is a four center study of women who undergo coronary angiography for suspected ischemia. In this cohort, 38% have significant CAD(>=50% stenosis in one or more epicardial arteries). At the baseline visit, 226 (48%) of 469 postmenopausal women indicated that they were on HRT during the previous three months. Women also reported psychological state with the Beck Depression Inventory (BDI)and the Cook Medley Scales. Higher scores on the BDI indicate more symptoms of depression, while higher scores on the Cook Medley indicate more hostility.
Results: Users of HRT were younger than non-users (60 yrs. vs. 64 yrs. respectively, p<0.001)and were more educated (55% vs.45%> high school). While among white women HRT use was associated with better psychological health, this effect was not apparent among black HRT users. BDI scores for white HRT users were 9.4 ± 7.8 vs. 10.6 ± 8.2 for non-users,(p=0.006, ajdusted for both age and education). Among black women, BDI scores were 13.0 ±8.2 for HRT users and 11.7 ± 8.0 for non-users, p=NS). Similar trends were noted for the Cook Medley Scores. Cook Medley Aggression scores were higher for non-users 2.9 ± 1.7 vs. 2.6 ±1.7 among white women (p< 0.001), but not black women. The Cook Medley scores for black women who used HRT were 3.2 ± 1.9 vs. 3.0 ± 1.7 for non-users (p=NS). Further adjustment of differences by angiographic findings (e.g. significant CAD)did not affect these associations.
Conclusion: In this cohort of women undergoing angiography for suspected ischemia, there are ethnic differences in the relationship between HRT use and psychological state. Within the white but not the black HRT users, there are fewer symptoms of depression and lower aggression scores than among the non-users.

1401 Sleep complaints increase the risk for recurrent events in middle-aged women with coronary disease. The Stockholm female coronary risk study

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Objective: Sleep disturbances have been found to increase coronary risk. Female coronary patients below the age of 70 have poorer prognosis compared to their male counterparts and women in general have more sleep problems than men. We examined the impact of sleep complaints on prognosis, taking into account both standard risk factors and depressive symptoms.
Methods: All female patients aged 65 or under who were admitted with an acute coronary syndrome between 1991 and 1994 in Stockholm, were followed for five years for recurrent coronary events (n=292). Sleep complaints and depression were measured at baseline using standardized questionnaires. The sleep questionnaire, which was answered by 283 women, assessed quality of sleep, restorative function of sleep and snoring.
Results: Poor sleep quality was associated with recurrent events including cardiovascular mortality, acute myocardial infarction and revascularization procedures. Adjusting for age, hypertension, diagnosis at index event, diabetes, body mass index, symptoms of heart failure, HDL-cholesterol, triglycerides, smoking and education, the hazard ratio for women with poor (upper quartile) as compared to good (lower quartile) sleep quality was 2.5 (95% CI: 1.2-5.2). Women who did not wake up refreshed, had a significantly higher multivariable risk of a recurrent events (HR=2.4; 95% CI: 1.2-4.6). We previously found a poorer prognosis in women with depressive symptoms (HR=1.9; 1.1-3,6). Women with both depression and poor sleep quality had 66% (95% CI: 59%-73%) event free survival compared to 83% (95% CI: 69%-97%) in women without any of these complaints (HR=2.7; 95% CI 1.1-7.1). Heavy snoring was not related to depression or to prognosis.
Conclusions: Our results indicate that poor sleep and not waking up refreshed predict poor prognosis in female coronary patients. The prediction was somewhat further strengthened by depressive symptoms.

1402 The impact of an implantable cardioverter defibrillator: the Leiden follow-up study of ICD patients and their partners

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Being a recipient of an implantable cardioverter defibrillator (ICD) might have considerable psychosocial consequences. This study therefore evaluated 1) the presence of psychosocial problems in ICD pts and 2) the relation between psychosocial problems and various clinical variables.
Methods Standardised questionnaires (also containing specific ICD related questions) were sent to 220 ICD pts. Chi-square tests were used for data analysis.
Results Sixty-eight percent of the ICD patients (123 male (81%), 59±12 yr.) and 62% of the partners (28 male (21%), 58±11 yr.) returned the questionnaires. Anxiety, depression or nervousness was reported by respectively 49%, 30% and 52% of the patients and by 36%, 24% and 66% of the partners. In patients, mental health problems were strongly associated with a lower left ventricular ejection fraction (p=0.006), younger age (p=0.029), employment (p=0.011), experience of ICD discharges (p=0.032), previous myocardial infarction (p=0.019) and a higher NYHA functional class (p=0.05). Use of psychiatric medication was related with female gender (p=0.014), experience of ICD discharges (p=0.044), older age (p=0.02), marital status (p=0.024) and co-morbidity (p=0.019).
In partners, nervousness was associated with previous myocardial infarction of ICD patients (p=0.049); the use of sedatives was associated with older age (p=0.017). Sixty percent of the partners had a need for counseling or support groups.
Conclusion: Psychosocial problems are present in ICD patients and their partners and are associated with a number of clinical variables. A specific ICD-rehabilitation program should therefore be available for both ICD patients and their partners.

1403 Working status after CABG and stented angioplasty: results from the ARTS study

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Background: The ARTS trial was a randomized clinical trial comparing bypass surgery with stented angioplasty. The results indicate that there are no differences in the incidence of death, MI and stroke but that stenting is associated with more repeat re-vascularizations. Despite these additional re-vascularizations stenting may still be associated with less medical costs. This present study aims to analyze the indirect non-medical costs associated with these different treatment strategies.
Method: To assess the working status of the patients, we reviewed information from the CRF for those patients below the age of 62 who were economically active at the time of procedure. A 'working' status variable was constructed, containing 5 levels; working, at home, in hospital, stopped working and dead. For each patient included the number of days spent in each 'status-value' was calculated. Analysis of variance for repeated measurements was used to assess the differences by treatment arm over time.
Results: Due to the difference in type of treatments, time spent in hospital and time at home are significantly higher in the CABG arm of the trial. The differences maybe translated into a cost of EUR 10,000 when valuing the days missed from work at a per diem of EUR 200 per day. All differences are concentrated during the first 6 months. The additional working days missed during follow-up in relationship to repeat procedures do not outweigh the differences in the first months.

	Mean days Stenting	Mean days Bypass	P-value
Death	15	26	0.393
Permanently stopped working	201	200	0.962
Time in hospital	8	12	0.0007
At home (temporarily not working)	95	140	0.0014
Working	780	722	0.169

Conclusion: The difference in working status, especially in terms of days worked, manifests itself in the first 6 months after the procedure. After 6 months, no significant differences are found and potential differences due to more repeat re-vascularizations do not outweigh the savings from the first six months.

MODULATION OF ATHEROSCLEROTIC PLAQUE INFLAMMATION

1412 The effects of azithromycin on soluble cell adhesion molecules and markers of inflammation: A randomized double blind placebo controlled study

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Background: Chlamydia pneumoniae (CP) infection has been implicated in the pathogenesis of atherosclerosis and the acute coronary syndromes (ACS). Macrolide antibiotics may reduce adverse events in survivors of an ACS, but the data are conflicting and the mechanisms unclear. One potential explanation is that macrolides reduce CP mediated activation of vascular endothelium, thereby reducing plaque instability. To test this hypothesis, the current study assessed the effects of azithromycin (AZ) on markers of endothelial cell activation (soluble cell adhesion molecules; sCAMs) and other inflammatory markers, in survivors of an ACS.
Methods: One hundred and forty one consecutive survivors of an ACS were studied 8 months after their index event. All had stable cardiac symptoms for at least 3 months prior to commencing the study. Patients were excluded if they had conditions known to affect levels of sCAMs +/or markers of inflammation. They were randomized to receive AZ 500mg daily for 5 days (n = 72) or matched placebo (n = 69). Neither patients nor investigators were aware of their treatment. Levels of soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1, soluble E-selectin, high-sensitivity C-reactive protein and interleukin-6 were assayed at baseline and 3 months later, along with CP titres (IgA and G). Baseline levels of sCAMs and inflammatory markers were correlated with clinical risk factors, CP titres and each other. Temporal changes in levels in active and placebo treated groups were compared using analysis of co-variance.
Results: Levels of sCAMs and inflammatory markers were significantly correlated with each other and with conventional risk factors but were unrelated to baseline CP titres. Mean levels of sICAM-1 fell in both placebo (baseline 304±10ng/ml, 3 month 290±9ng/ml) and AZ treated (baseline 307±11ng/ml, 3 month 277±10ng/ml) patients during the study period, but this was more marked in the group who received active treatment (adjusted difference in means 19.4; 95% CI 3.9 - 34.9: P = 0.01). AZ treatment had no significant effect on levels of other sCAMs and inflammatory markers.
Conclusion: Among survivors of an ACS, CP seropositivity is not associated with higher levels of sCAMs or other inflammatory markers. AZ reduces sICAM-1 levels but not other sCAMs or inflammatory markers. It is not, however, clear that the modest effect demonstrated would be of clinical relevance. Further study is required to explain these data, to determine the effects of prolonged therapy and to assess any impact of AZ on leukocyte activation

1413 Interleukin-10 production is decreased in activated monocytes from patients with acute coronary syndromes

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Objectives To investigate if activated monocytes in acute coronary syndromes (ACS) produce different amounts of cytokines that are known to affect the Th1/Th2 balance.
Background ACS are associated with enhanced monocyte activation. Monocyte activation in ACS is supposedly the result of the action of pro-inflammatory (Th1-type) cytokines. However, not much is known about the role of anti-inflammatory (Th2-type) cytokines.
Methods C-reactive protein (CRP) and neopterin levels were measured in 22 patients with acute coronary syndromes, 50 patients with stable vascular disease and 22 healthy controls. In addition, levels of TNF-alpha and Il-10 were determined after repectively 6 hours and 24 hours of incubation of full blood with lipopolysaccharide (LPS, 50 μg/mL).
Results As expected, CRP (median, interquartile range (IQR)) (1.5 mg/L(0.8-4.5) vs. 2.1(0.9-3.6) vs. 0.4(0.3-1.2)) ($p<0.001$) and neopterin (7.4 nmol/L(6.0-8.7) vs. 7.1(6.0-8.9) vs. 6.4(5.6-7.3)) (p=0.07) were higher in patients with atherosclerosis than in controls. IL-10 production after LPS stimulation was greatly reduced in patients with acute coronary syndromes (16,175 pg/ml, 7,559-28,470 pg/ml) as opposed to patients with stable atherosclerosis (28,379 pg/ml, 12,601-73,968 pg/ml) and healthy controls (63,830 pg/ml, 22,040-168,000 pg/ml) (p=0.003). Levels of TNF-alpha were not different (7,313 pg/ml(4,740-12,615) versus 11,002(5,913-14,190) versus 8,229(5,225-11,364) (p=0.24).
Conclusions Inflammation in unstable atherosclerosis is associated with monocyte activation and a reduced production of IL-10. We hypothesize that, in unstable coronary syndromes, the production of Th1 cytokines that are responsible for the activation of monocytes/macrophages is not counterbalanced by anti-inflammatory cytokines such as IL-10, thus favoring inflammation and thrombosis.

1414 Cytokine mRNA expression is significantly increased in diseased vein grafts specimen compared to native veins or coronary artery disease

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Background: Elevated cytokines levels in atherosclerotic lesions may contribute to plaque vulnerability with unstable plaque syndromes and subsequent vessel occlusion. To what extent inflammation contributes to vein graft disease is widely unknown. Therefore, the mRNA expression of various cytokines (IL -1, IL -6, IL -8, TNF-a, INF-?) were quantified in diseased vein graft specimen and compared to cytokine mRNA levels in native saphenous veins and atherosclerotic coronary arteries.
Methods and Results: Cytokine mRNA expression was quantified using a real time RT-PCR in the following tissue samples immediately snap frozen during cardiac surgery: native saphenous veins (nSV), coronary arteries with atherosclerotic changes (CAD) and diseased vein grafts (VG).
Diseased vein grafts expressed significantly higher cytokine m RNA levels compared to nSV resp. CAD specimen (Il-1: p= 0.003 resp. p=0.012; IL-6: p=0.009 resp. p=0.0004; IL-8: p= 0.001 resp. p= 0.001; TNF-a: p= 0.017 resp. p= 0.023) No differences regarding INF-? mRNA expression could be detected between the studied tissue specimen.
Conclusion: Cytokine mRNA expression of IL-1, -6, - 8 and TNF-a was significantly increased in diseased vein grafts compared to native saphenous veins and coronary artery disease. Thus vein graft disease seems to have a pronounced inflammatory activity. This finding may implicate new therapeutic strategies for the prevention of the unresolved problem of vein graft disease.

1415 Human Toll like receptor 2 activation results in expression of pro-inflammatory factors associated with plaque vulnerability

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Toll Like Receptor-2 (TLR-2) is a member of the Toll like receptor family which is an essential part of the innate immune system. TLR-2 is the specific receptor for the Gram + bacterial cell wall component peptidoglycan (PG). We recently detected PG in human atherosclerotic plaques and observed an association between its presence and plaque vulnerability. We hypothesize that arterial wall cells can be activated by PG through TLR-2 leading to the production of pro-inflammatory factors, favoring plaque instability. Human coronary arteries as well as human vascular smooth muscle cells (VSMC) and primary adventitial fibroblasts (PAF) were analyzed for the expression of TLR-2 and stimulated with PG to study the expression of pro-inflammatory cytokines and chemokines.

Methods: TLR-2 was detected by Western-blot in human coronary arteries and cells. Cultured VSMC (cell-line) and PAF (isolated from fresh human aorta) were stimulated for 6 hours with 15 μg/ml PG. Expression of pro-inflammatory cytokines were detected on mRNA and protein level using a RNAse protection assay and ELISA technique.

Results: Western-blot analyses revealed the presence of TLR-2 in human coronary artery tissue and in cell-lysates from PAF and VSMC. TLR-2 expression did not increase in cells after PG stimulation. Cytokine and chemokine production did increase following PG stimulation, as is depicted in the table.

	VSMC mRNA (OD*mm²)		PAF mRNA (OD*mm²)		PAF protein (ng/ml)	
	PG	control	PG	control	PG	control
IL-1 beta	0,5±0,1	0,4±0,1	12,6±4,5*	2,4±0,4	3,3±0,3 *	1,5±0,1
IL-1 Ra	70,9±19,4*	13,3±9,6	51,0±10,2*	0,13±0,6	0,3±0,1 *	ND
IL-6	50,8±9,8*	12,5±7,8	70,6±9,1*	9,1±2,7		
IL-8	6,7±1,7*	2,2±0,4	21,0±3,6*	0,4±0,3		
MCP-1	1,1±0,1	1,3±0,1	91,6±12,6	4,9±0,9		

Cytokine and chemokine expression in cultured cells after PG stimulation. ND=non detectible; *=P< 0,05 compared with control; n=3

Conclusion: We report, for the first time, the presence of TLR-2 in human coronary arteries and in cells originating from the vascular wall. Our data show that cells in the arterial wall can be activated through TLR-2 to produce pro-inflammatory cytokines/chemokines. Therefore, TLR-2 may be an important mediator in the inflammatory process, leading to plaque vulnerability.

1416 Oestrogen's protective effect against atherogenesis may be mediated by an up-regulation of interleukin-10 production

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The protective role of oestrogen against early development and progression of atherosclerosis is well documented, but the mechanisms responsible for this effect are not well understood. Atherosclerosis has recently been recognized as an inflammatory process and interleukin-10 (IL-10) is a potent anti-inflammatory cytokine with a number of potential effects that could dampen inflammation at sites of vascular wall damage. Thus, we studied the effects of 17beta-oestradiol on IL-10 production by peripheral blood mononuclear cells (PBMC) of postmenopausal women. Forty healthy postmenopausal women, age range 50-65 years, with clinical symptoms of oestrogen deficiency were enrolled in the study. The control group consisted of twenty healthy young women, age range 22-31 years, with regular menses and who were not taking oral contraceptives. The levels of IL-10 in the sera and PBMC culture supernatants were measured using commercially available immunoassay. The effect of 17beta-oestradiol on the spontaneous IL-10 production by PBMC of postmenopausal women was also studied in vitro and in vivo. Thirty out of forty postmenopausal women were given hormonal replacement therapy of 50μg 17beta-oestradiol/day transdermally (Estraderm 50MX, Novartis) and the spontaneous production of IL-10 by the PBMC was analysed after 6 and 12 months of treatment. The postmenopausal women had significantly lower serum levels of IL-10 than the young controls. The spontaneous production of IL-10 by non-stimulated PBMC into the culture supernatants was also significantly lower in the postmenopausal women compared with the young. Our in vitro experiments showed that 17beta-oestradiol at the concentrations of 10-8M up-regulated the spontaneous IL-10 production by PBMC of postmenopausal women. In vivo treatment with 17beta-oestradiol transdermally also enhanced spontaneous IL-10 production by PBMC of postmenopausal women after 12 months of the therapy. Our results indicate that 17beta-oestradiol may enhance IL-10 production by the PBMC of postmenopausal women. We suspect that one of the mechanisms of oestrogen's protective effect against atherogenesis may be mediated by an up-regulation of IL-10 production - a potent anti-inflamatory cytokine with anti-atherogenic properties.

YOUNG INVESTIGATORS' AWARD SESSION (THROMBOSIS)

1432 NFkB and IkB kinase-2 regulate tissue factor and cytokine production in human atherosclerotic plaques: an analysis via adenoviral gene transfer

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Background Nuclear translocation of nuclear factor kappa B (NFkB) subunit p65 has been observed in human atherosclerotic plaques. However it is difficult to test in vivo if NFkB activation is necessary for tissue factor (TF) and cytokine production in atherosclerotic plaques, due to the lethality of p65 and I kappa B alpha (IkBa, the inhibitor of NFkB nuclear translocation) knock-out mice. Adenoviral gene transfer can be used to overcome these limitations and dissect intracellular signalling pathways. The aim of our study was to achieve direct evidence of a functional requirement for NFkB and IkB kinase-2 (IKK-2), the main kinase responsible for IkB phosphorylation and degradation, in the regulation of cytokine and TF production in human atherosclerotic plaques.

Methods Atherosclerotic tissue, obtained from aorta, carotid, iliac, femoral and popliteal arteries from patients undergoing revascularisation/repair surgery, was dissociated via enzymatic digestion in order to obtain a single cell suspension, cultured and infected with adenoviral vectors encoding for beta-Galactosidase (Adv-bGal), for IkBa, for the dominant negative (DN) form of IKK-2, or without insert as control. TF antigen was assessed by ELISA on cell lysates. IL-6 and TNFalpha production was assessed via ELISA in culture supernatants.

Results Enzymatic dissociation yielded a viable population of cells, containing lymphocytes (CD3+, range 6-17%), macrophages (CD68+, 40-50%) and smooth muscle cells. Cells remained viable in culture until at least day 5, and showed a constitutive production of TF (2100pg/mL±995 at 24 hours), IL-6 (6049pg/mL±7000) and TNFalpha (800pg/mL±623). Successful infection with Adv-bGal of >90% of cells was achieved at a multiplicity of infection as low as 100:1, as evaluated by FACS analysis. Overexpression of IkBa (as assessed by Western Blot) abolished spontaneous expression of TF, and significantly reduced constitutive production of TNFalpha by 90±16% and IL-6 by 75±17% ($p<0.001$). Similar results were obtained by overexpression of DN IKK-2.

Conclusions Cells freshly isolated from atherosclerotic plaque in culture constitutively produce TF and pro-inflammatory cytokines such as TNFalpha and IL-6. We have established a method of adenoviral gene transfer into these cells resulting in high infectibility rates. Constitutive production of TF and cytokines could be strongly inhibited by adenovirally-mediated NFkB and IKK-2 blockade. Thus, NFkB and IKK-2 appear to be interesting potential therapeutic targets for treatment and prevention of atherosclerosis and its thrombotic complications.

1433 Synthetic peptide-analogues of the GPIIb subunit inhibit fibrinogen binding to the GPIIb/IIIa receptor and platelet activation

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Background and Aim: Upon platelet activation the integrin receptor GPIIb/IIIa, undergoes conformational changes and binds to soluble adhesive ligands, mainly fibrinogen (Fg), leading to platelet aggregation. The GPIIb/IIIa ligands contain the recognition sequence, Arg-Gly-Asp (RGD). RGD containing peptides and non-peptide mimetics are potent inhibitors of GPIIb/IIIa-Fg interactions, however, they maintain the receptor in its high affinity state, enhancing platelet activation, through an outside-in signaling pathway. An alternative approach for inhibiting Fg binding to GPIIb/IIIa, platelet aggregation and further enhancement of platelet activation, is to use peptide analogues of the GPIIb/IIIa binding sites for Fg that could interact with Fg, and inhibit its binding to the receptor.
Methods and Results: Five 20-peptides, overlapping by eight residues, covering the extracellular sequence 289-356 of the GPIIb subunit were synthesized. Their effect on ADP-induced platelet aggregation and ATP secretion was studied. The effect of these peptides on the binding of FITC-labeled Fg (FITC-Fg) to ADP-activated platelets, as well as on the binding of the specific antibody PAC-1 against the activated receptor was also determined by flow cytometry. Among them, the 20-peptide 313-332 (YMESRADRKLAEVGRVYLFL) exhibited the most potent inhibitory effect on platelet aggregation (56% inhibition) and ATP secretion (100% inhibition). Furthermore, the peptide completely inhibited the binding of FITC-Fg on ADP activated platelets, whereas it did not affect the binding of PAC-1. To further investigate the amino acid sequence responsible for this effect, we synthesized several 8-peptide analogues of the above sequence. Our results showed that peptides containing the ESRAD sequence maintained the inhibitory properties exhibited by the original 20-peptide. The RGDS peptide that is known to bind to the receptor inhibited platelet aggregation and ATP secretion, as well as the binding of FITC-Fg and PAC-1.
Conclusions: The 20-peptide analogue 313-332 of the GPIIb subunit inhibits platelet aggregation and secretion possibly interacting with fibrinogen rather than the receptor itself in contrast to RGDS, which inhibits platelet aggregation, interacting with the receptor. This effect is possibly due to the amino acid sequence ESRAD. Such peptides may be useful tools in the further understanding of the interactions between GPIIb/IIIa and Fg, which lead to platelet aggregation and activation, or may be used as potent inhibitors of platelet activation.

1434 The PPAR-gamma agonist rosiglitazone reduces circulating platelet activity in non-diabetic coronary artery disease patients

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Background: Platelet activation plays a key role in atherogenesis, the genesis of atherothrombotic events and the pathogenesis of restenosis after coronary artery stenting. Rosiglitazone, a Peroxisome Proliferator-Activated Receptor-gamma (PPAR-gamma) agonist, is an insulin-sensitising agent and is used in the treatment of type 2 diabetes mellitus. Recent studies suggest that PPAR-gamma agonists may have direct anti-inflammatory and anti-platelet effects, independent of their insulin-sensitising effect. The aim of this study was to assess the effect of rosiglitazone on circulating platelet activity in non-diabetic coronary artery disease patients.
Methods: Ninety-two subjects with stable, documented coronary artery disease and without previously diagnosed type 2 diabetes mellitus were selected. Maintaining their current therapies, patients were randomised in a double-blind manner to placebo (n=46) or rosiglitazone (n=46, 4 mg/day for 8 weeks followed by 8mg/day for 4 weeks) for 12 weeks. Circulating platelet activity was measured at baseline and after 12 weeks using whole blood flow cytometry to quantify the percentage of platelets expressing P-selectin (CD62P). Fasting insulin and glucose were also measured at baseline and at study end. The homeostasis model of insulin resistance index (HOMA-R) was used as a measure of insulin resistance where HOMA-R is calculated as fasting serum insulin * fasting plasma glucose/22.5. One way ANOVA for repeated measurements was used to assess the effect of treatment on measured parameters.
Results: Eighty-four subjects completed the study. The % of P-selectin positive platelets was significantly reduced by rosiglitazone treatment compared with placebo (P = 0.04). In the rosiglitazone group the % of P-selectin positive platelets (median [interquartile range]) decreased from 0.1% [0.05-0.24] to 0.05% [0.01-0.15]. Rosiglitazone treatment also significantly reduced insulin resistance (HOMA-R) compared to placebo (P = 0.023). No significant correlation was observed between change in platelet activity and change in HOMA-R or fasting glucose.
Conclusions: We have shown for the first time that rosiglitazone significantly reduces circulating platelet activity in coronary artery disease patients without diabetes mellitus. This effect appears to be independent of any insulin-sensitising or glucose lowering effect. Further studies are warranted to determine whether this anti-platelet effect translates into clinical benefit, namely a reduction in the risk of atherothrombotic events, in both diabetics and non-diabetics.

1435 Intravenous infusion of a nitric oxide donor inhibits thrombosis triggered by damaged vessel wall at flow conditions of coronary arteries

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Background: Impairment of nitric oxide (NO) dependent pathways have deleterious effects in the cardiovascular system because of the multiple processes that are regulated by NO. Compounds that release NO are useful candidates to restore NO-functions in specific pathological situations.
Objective: To study whether donation of NO with a novel platelet-selective NO-donor (LA-810) at a systemic level can inhibit thrombosis elicited by damaged vessel wall (eroded and disrupted vessel wall) at hemodynamic conditions typical of patent and stenotic (60 to 70%) coronary arteries.
Methods: Thrombogenicity was measured at baseline and after intravenous injection of a NO-donor in the porcine experimental model and assesed as platelet-thrombus formation in the ex vivo Badimon perfusion chamber. Animals were anesthetized, heparinized, catheterized and the perfusion chamber was placed in an extracorporeal shunt (carotid artery-jugular vein). After baseline perfusions, pigs were given the iv-infusion of NO donor (6.6 nmols/Kg/min at an infusion rate of 1.25 ml/min) during 2 hours. Platelet deposition was quantified by radioisotopic measurement of deposited platelets. Blood pressure, heart rate and in vitro platelet aggregation were measured during all the experiments.
Results: Platelet deposition was significantly inhibited ($p<0.0005$) on both disrupted and eroded vessels and at shear rates typical both of patent and stenotic coronaries, without significant modifications of blood pressure or heart rates.Platelet aggregation in vitro was also inhibited. Platelet deposition on severely damaged vessels was reduced from $98x10^6$ to $47x10^6$ PTL/cm^2 ($p<0.0001$) at stenotic shear rate and from $54x10^6$ to $28x10^6$ PTL/cm^2 ($p<0.0001$) at patent artery shear rate. Platelet deposition on eroded vessels (mild injury) was reduced from $11x10^6$ to $6x10^6$ PTL/cm^2 ($p<0.0001$)at stenotic shear rate and from $3x10^6$ to $1x10^6$ PTL/cm^2 ($p<0.0001$) at patent artery shear rate.
Conclusions: Donation of NO with a novel NO-donor,that without modifying blood pressure inhibits platelet function, is a highly efficacious antithrombotic strategy at all shear rates and degrees of vascular damage. Therefore, it seems a highly promising strategy to reduce acute thrombosis triggered by coronary artery disease.
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1436 Proteolysis of tissue factor pathway Inhibitor-1 by thrombolysis in acute myocardial infarction

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In acute myocardial infarction (AMI), surface-bound TFPI-1 inhibits an increased monocyte procoagulant activity. In addition, TFPI-1 is released from microvascular endothelial cells after treatment with heparin and thereby contributes to its antithrombotic properties.
We examined 19 patients of a randomized study comparing intravenous fibrinolysis with atleptase (n=9) and revascularization by stent placement (n=10). Before and after therapy we obtained blood samples for analysis of monocytic TFPI-1 surface expression by flow cytometry and plasma TFPI-1 concentrations by immunoassay.
We found a significant decrease in surface TFPI-1 on circulating monocytes 24 hours after thrombolysis (P=0.006) that was not observed after stenting. Systemic plasma TFPI-1 concentrations increased immediately after stenting by 71±14% (P=0.008) whereas after thrombolysis, a decrease in TFPI-1 plasma concentrations by 21±11% was observed (P=0.075). In vitro experiments confirmed that plasmin decreased TFPI-1 surface expression dose-dependently.
Activation of the fibrinolytic system by atleptase in AMI decreases surface-associated TFPI-1 on circulating monocytes and plasma TFPI-1. Reduced TFPI-1 may contribute to thrombotic complications after fibrinolysis in AMI.

CORONARY REVASCULARISATION: NEEDLE OR KNIFE?

1446 Arterial revascularization therapy study: a randomized trial of stenting in multivessel coronary disease versus bypass surgery. 3 year results

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Background: The ARTS study showed that, after 1 year, CABG was 14% more effective but also EUR 3,000 per patient more costly, suggesting that stenting may be preferred over CABG in patients for whom both treatments seem appropriate.
Methods: Twelve hundred and five patients were randomly assigned to bypass surgery or stent implantation when there was consensus between the cardiac surgeon and interventional cardiologist on equivalent 'treatability'. The primary clinical endpoint was freedom from major adverse cardiac and cerebrovascular events at one year. Major adverse cardiac and cerebrovascular events at 3 years constitute a secondary endpoint. Cost is expressed as resource use multiplied by unit costs. Effectiveness is expressed as freedom of Major Adverse Cardiac and Cerebrovascular events. Cost effectiveness is the ratio of both parameters, the difference in cost and effect were evaluated.
Results: At three years 95.5% of the surgical group and 96.3% of the stented patients were alive (p=0.56). Eighty eight (88.8) % of the surgical and 87.0% of the stented patients were free of death, stroke and myocardial infarction (P=0.38). Among patients who survived without stroke or myocardial infarction, 21.3% underwent a second revascularization in the stent group, as compared with 5.1% in the surgical group. At three years 83.6% of the surgical and 65.7% of the stented patients were event-free survivors (P <0.001). At three years 87.0% in the surgical cohort and 81.6% in the stent group were angina free. In patients with diabetes 81.3% in the surgical group and 52.7% in the stented patients were free of any events after three years (P <0.001). The ARTS study showed that, after 3 years, CABG was 18% more effective but also EUR 2,268 per patient more costly, resulting in an incremental cost effectiveness ratio of EUR 9,996.
Conclusion: The difference in the rate of revascularization between the two groups was 15% at 2 years and is 18% at 3 years. At three years the percutaneous treatment is no longer more cost effective than the surgical treatment.

1447 De novo proximal–mid-LAD lesions: a comparison of minimal invasive direct coronary artery bypass (MIDCAB) with coronary artery stenting

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Background: MIDCAB and coronary artery stenting are established methods of treatment for isolated lesions of the left anterior descending artery (LAD). We compared the two methods in a matched patient population in a single center setting.
Methods: We evaluated the in-hospital and one-year results in 119 consecutive patients who underwent MIDCAB to 441 consecutive patients undergoing coronary stenting in isolated proximal and mid LAD lesions. We excluded patients with acute MI, shock, and severe heart failure.
Results: In-hospital complications were similar between MIDCAB and stenting; but surgery had longer length of hospital stay. At one-year follow-up, MACE and target vessel revascularization (TVR) were higher in the stent group, whereas 1-year mortality was similar in both groups.

In-hospital and 1-year clinical outcome

	MIDCAB	Stent	P value
IH-death	0.0%	0.9%	0.6
IH QWMI	0.0%	0.5%	1.0
IH non-QWMI	9.2%	10.7%	0.7
IH MACE	0.8%	1.4%	1.0
IH stroke	0%	0.5	1.0
Hospital length of stay (days)	8.8 ± 3.3	3.0 ± 3.7	0.06
ICU length of stay (days)	1.1 ± 0.7	0.2 ± 1	<0.0001
1-year death	3.1%	3.4%	1.0
1-year MI	0.0%	2.3%	0.21
1-year TVR	7.2%	16.8%	0.01
1-year MACE	3.1%	18.4%	0.0005

Conclusions: MIDCAB and coronary artery stenting have very similar in-hospital and death and MI rates. MIDCAB requires longer hospitalization, but has less TVR and MACE at 1-year than the current stent designs. However, 1-year mortality of stenting is similar to MIDCAB.

1448 Primary stenting or ACAB? Early results of comparison the two methods of treatment of single LAD disease

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100 patients aged 25-76(mean age 52),with anginal symptoms of at least CCS II, and angiographically proved critical stenosis of proximal segment of LAD, were randomised to primary, direct stenting (DS, 50 patients, group I), or atraumatic, coronary artery bypass grafting, by the use of thoracoscopic harvested left internal mammary artery (ACAB, 50 patients, group II).
Coronary artery risk factors, mean age, left ventricle ejection fraction, type of lesion and degree of LAD stenosis were comparable in both groups.
Optimal angiographic and clinical result was obtained in group I, with no in-hospital complications, and no adverse events in one month follow-up period. 6-months follow-up comprised 40 patients, whose anginal and angiographic status was evaluated, resulting in 15% rate (6 patients) of restenosis, that was treated with PTCA.
In group II, we achieved a very good effect, with no relevant complications during in-hospital and 1-month follow-up period. From 40 patients, whose clinical status was assesed in 6-months follow-up, non symptomatic critical stenosis of LIMA-LAD anastamosis was observed only in 1 case (2,5%) –PTCA of the graft was performed.
One-year clinical follow-up included 22 patients of group I, mean anginal status was CCI I, stress test was negative in 19 patients, positive in 3 patients (13,6%), who required target vessel revascularisation procedures. One death was noted due to disseminated neoplasmatic disease. During one –year follow-up of 22 patients from group II, only one patient (4,7%) had aggraviation of anginal status, a control angiography revealed coronary artery disease progression, (PTCA of RCA was performed). Other patients from group II had no angina in one-year follow-up.
Conclusions: early results show a definitive prevalence of cardiosurgical treatment (ACAB), upon direct primary stenting of LAD critical stenosis, with only slightly higher cost of surgical procedure.

1449 Assessment of left ventricular function in patients 1 year after randomisation to coronary artery bypass graft surgery or stent percutaneous coronary intervention in the SoS trial

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Background In the Stent or Surgery study (SoS), patients were prospectively randomised to CABG (500) and PCI (488) with stent implantation aiming for optimal revascularisation. We hypothesised that LV function at 1 year post - procedure will be the same, regardless the initial treatment allocation.
Methods: Global LV function was assessed by ejection fraction (EF) (modified Simpson's rule), and regional LV function by the wall motion score Index (WMSI) (ASE), using echocardiography. Echocardiographic studies were analysed blindly at a core laboratory. Primary outcome was a comparison of WMSI and EF at one year between the two groups.
Results Of the 988 patients randomised, 972 (98.4%) were alive at one year. In the surviving patients 764 (79%) had available WMSI calculations and 515 (53%) had EF measured at one year. The WMSI in the CABG group (n=383) was 1.3 (SE 0.2), compared with 1.2 (SE 0.2) in PCI group (n=381), P=0.48). The EF in the CABG group (n=245) was 54.8 (SE 0.6), compared with 55.3 (SE 0.6) in PCI group (n=270), difference =0.5, 95% CI -1.1 to 2.1, P=0.55. Compared with the pre procedural values both groups showed a similar change in WMSI and EF. The WMSI was greater at 12 months: CABG group 1.19 versus 1.27, (mean difference 0.08, 95% CI 0.04 to 0.11, p<0.001), PCI group 1.19 versus 1.26 (mean difference 0.07, 95% CI 0.03 to 0.10). EF was lower in both groups: CABG group 57.5 versus 54.9, (mean difference -2.7, 95% CI -4.0 to -1.4, p<0.001), in the PCI group 56.7 versus 54.9 (mean difference -1.9, 95% CI -2.9 to -0.8, p=0.001).
Conclusions In the SoS study at one year there was no difference in LV function in patients treated with PCI or CABG. At one year there has been a minor decline in global and regional function which may be attributable to the occurrence of myocardial infarction and other factors affecting cardiac function.

1450 Fractional flow reserve to select optimum treatment in multivessel disease: beyond ARTS

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Background: In multivessel disease, it is controversial if complete revascularization by bypass surgery (CABG) is superior to PTCA of the culprit lesion(s) only. Fractional flow reserve (FFR, calculated from coronary pressure measurement) is a reliable index to identify whether a stenosis is culprit (i.e. functionally significant). Aim of the present study was to compare selective PTCA of culprit lesions only (FFR less than 0.75) to CABG of all stenoses.
Methods: In 150 patients with ARTS-like characteristics, referred for CABG, FFR was determined in 378 coronary arteries considered for bypass grafting. If FFR was less than 0.75 in 3 or more stenoses or in 2 type C lesions, CABG was performed (CABG-group). If only 1 or 2 lesions (not both type C) were culprit, PTCA and stenting of those lesions was performed (PTCA-group).
Results: Out of 150 patients, 86 classified for CABG-group and 64 for PTCA. Both groups had complete similar angiographic and other baseline characteristics. At 2-year follow-up, no differences were seen in adverse events (event free survival 74% in CABG-group and 72% in PTCA-group) and a similar number of patents were free from angina (76% in the CABG-group and 77% in the PTCA-group). Importantly, the results in both groups were as good as the surgery group in the ARTS-study.
Conclusion: In patients with multivessel disease, PTCA of culprit lesion(s)only, as identified by FFR below 0.75, yields a similar 2-year outcome as bypass surgery.

1451 Minimally invasive CABG versus PTCA with stenting in isolated high-grade stenosis of the proximal LAD

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Purpose: To compare minimallly invasive direct coronary artery bypass grafting (surgery) with percutateous transluminal coronary angioplasty with primary stenting (stenting) in patients with an isolated high grade stenosis (ACC/AHA classification type B2 or C) of the proximal left anterior descending artery (LAD). At 6 months both procedures are compared in a single centre prospective, randomized study with angiographic and clinical follow-up.
Methods: Patients with stable angina pectoris due to an isolated high grade stenosis of the proximal LAD were randomly assigned to surgery (n=51) or stenting (n=51).
Results: Periprocedural events did not significantly differ between surgery and stenting. At 6 months quantitative coronary angiography showed a patency rate of 96% after surgery and 71% after stenting ($p<0.001$). After 6 months no significant difference was found for major adverse cardiac or cerebral events (MACCE) and need for repeat target revascularisation between surgery and stenting. After 6 months return of angina pectoris and physical work capacity did not significantly differ between both procedures. However, use of antianginal drugs was significantly higher after stenting (<0.01).
Conclusion: This is the first prospective, randomized study that shows that in patients with a high grade stenosis of the proximal LAD, minimally invasive direct coronary artery bypass grafting (MID-CABG) has a significantly better patency rate and a lower need for antianginal medication, than percutaneous transluminal angioplasty (PTCA) with stenting after 6 months follow-up.

DRUG ELUTING STENTS: ARE THEY STILL HOLDING THEIR PROMISE?

1452 365-day follow-up of the RAVEL study: a randomized study with the sirolimus-eluting bx velocityTM balloon-expandable stent

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Background: The RAVEL is a multicenter, double-blind, randomized study with a two-arm design assessing safety and effectiveness of the Sirolimus-eluting Bx VelocityTM stent versus the uncoated metal Bx VelocityTM stent (18 mm).
Methods: The primary endpoint was angiographic late loss at 6 months. The secondary endpoints were major adverse cardiac events (MACE), target vessel revascularization, target lesion (TL) revascularization, restenosis rate. Inclusion criteria: patients with stable or unstable angina with single treatment of de novo lesions, < 18 mm in length, 2.5-3.5 mm in diameter.
Results: Between August 2000 and December 2000, 238 patients were included in 19 sites in Europe and South America. Baseline demographics and lesion characteristics were equally distributed. After a loading dose, Clopidogrel or Ticlopidine was continued up to 8 weeks. No acute, subacute or late thrombosis occurred. During a follow-up to 1 year, the overall rates of rank-ordered MACE were 5.8 percent in the actively treated group versus 28.8 percent in the control group ($p<0.001$) (table).

	Sirolimus		Control	
	210 days	365 days	210 days	365 days
Death	0	2 (1.67%)	2 (1.69%)	2 (1.69%)
Q-wave MI	2 (1.67%)	2 (1.67%)	0	0
Non Q MI	1 (0.83%)	2 (1.67%)	3 (2.54%)	4 (3.39%)
TL CABG	1 (0.83%)	1 (0.83%)	1 (0.85%)	1 (0.85%)
TL PTCA	0	0	26 (0.85%)	27 (22.88%)
Any MACE	4 (3.33%)	7 (5.83%)	32 (27.2%)	34 (28.8%)

Conclusions: The cumulative event-free survival is 94.0% in the Sirolimus group versus 70.7% in the control group ($p<0.001$).

1453 The U.S. multicenter, randomized, double-blind study of the sirolimus-eluting stent in coronary lesions: safety outcomes at 9 months

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SIRIUS is the U.S. multicenter (53 investigational sites), randomized, double-blind study examining the safety and efficacy of the Sirolimus-eluting coronary CYPHER stent (140mcg sirolimus/cm^2, slow-release) vs. placebo (conventional, bare metal VelocityTM coronary stent) in 1,101 patients (550 pts per arm) in de novo native coronary lesions. Single vessel treatment of "higher risk" lesions – 2.5-3.5mm diameter and 15-30mm length – is required. Antiplatelet regimen consists of ASA + Plavix (for 12 weeks). The primary endpoint is target vessel failure at 9 months (cardiac death, MI, or target vessel revascularization). Repeat angiography at 8 months (first 850 pts) and intravascular ultrasound substudy are secondary endpoints. Patients enrollment was complete in August 2001.
There were no differences in baseline demographic characteristics between the 2 groups. Diabetic patients contributed to 26.5% of all randomized patients. Patient demographics, lesion characteristics, and acute procedural angiographic and clinical results were similar between the two groups. Major adverse cardiac events, (MACE: Death, MI, Target vessel revascularization) at 30-days are presented in the table. No cases of acute stent thrombosis were reported at 180 days of follow-up. There were 2 cases of subacute stent thrombosis and one late thrombosis in all randomized patients.

MACE at 30-days

	Group A (n=522)	Group B (n=535)
Death (%)	0	0.2
CABG (%)	0	0
Q-wave MI (%)	0	0.4
Non-Q wave MI (%)	2.1	2.1
Repeat PCI (%)	0	0
30-days MACE (%)	2.1	2.8

CABG = coronary artery bypass grafting; PCI = percutaneous coronary interventions

Conclusion: The SIRIUS study represents a higher risk study cohort than RAVEL. The incidence of stent thrombosis seems to be low at 180-days of follow-up. Fully adjudicated rates of stent thrombosis (acute, subacute and late), death and MI at 9 months for the entire study cohort will be available for presentation.

1454 A European multi-centre, randomised, double-blind study of the sirolimus-eluting stent in patients with de novo coronary artery lesions

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Background: Long-term results after coronary stenting are limited by excessive neointimal hyperplasia resulting in restenosis and repeat revascularization. Sirolimus (rapamycin), a macrolytic immunosuppressant with cytostatic and anti-inflammatory actions, incorporated within a non-reactive polymer coating has been shown to reduce neointimal hyperplasia in pre-clinical and clinical research.
Methods: The E-SIRIUS study is a multi-centre (35 investigational sites in Europe) randomised, double-blind trial examining the safety and efficacy of the sirolimus-eluting stent vs. a control (uncoated) stent in 350 patients (175 patients per study arm) with de novo native coronary artery lesions >= 15 and <= 32 mm in length and >= 2.50 mm to <= 3.0 mm in diameter (by visual estimate). Antiplatelet regimen is 60 days of clopidogrel with long term ASA. The primary endpoint is in-stent minimum lumen diameter (MLD) at 8-month follow-up. Secondary endpoints will be assessed as composite Major Adverse Cardiac Events at 30 days, 6, 9, and 12 months, and 2, 3, 4 and 5 years post-procedure. Other secondary endpoints include angiographic binary restenosis (>= 50% diameter stenosis) at 8 months post-procedure. The secondary objective is to assess cost-effectiveness expressed in incremental cost/life years gained or cost/quality adjusted life year gained at different time points (8 months, 1 year, 3 and 5 years).
Results: Thus far (as of February 1, 2002), 339 patients have been enrolled in the study as per protocol.
Conclusions: A multi-centre, European, randomised, double-blind trial to determine the safety and effectiveness of the sirolimus-eluting stent in de novo native coronary artery lesions (E-SIRIUS) is underway. Thirty-day results from the enrolled patient cohort focusing on safety issues will be available for presentation.

1455 Study of anti-restenosis with the biodivysio dexamethasone eluting stent (STRIDE) – a multicenter trial

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Background: Drug eluting stents have been proposed as an alternative approach to prevent in-stent restenosis. Pre-clinical work showed a reduced intimal hyperplasia in a porcine model using the Biodivysio Drug Delivery Phosphorylcholine coated stent loaded with a high dose dexamethasone (DEX). The aim of this study is to evaluate the acute safety and efficacy of the Biodivysio DEX eluting stent implanted in patients with de novo single vessel disease.
Methods: In this multicenter trial, 71 patients, 79% were male, average age 61.9 (range 42 - 82) from 8 study sites were included. Risk facters: 63% had hypercholesterolaemia, 56% had hypertension, 42% had a previous MI, 46% had two or more than two vessel diseases, 31% had lesion type B2 or C, 28% had unstable angina pectoris. One 11 mm, 15mm or 18mm long Biodivysio DD PC stent was immersed in a 15 mg/ml DEX solution, yielding a total DEX dose of 45 μg per mm stent before implantation. Minimal lumen diameter (MLD) and % diameter stenosis (DS) were measured before, immediately after stenting and at 6-month (m) follow-up (f-up). The primary endpoint of the study is 6m angiographic restenosis rate. The secondary endpoints are 30 days and 6m major adverse cardiac events (MACE) defined as death, MI, CABG & target vessel revascularization.
Results: All the stent implantations were successful. Five pts were excluded from further analysis because of obvious protocol violations. Per protocol MACE at 6m: 2 pts had recurrence of symptoms, due to a study stent related restenoses (2.8%). QCA: mean reference diameter: 2.95±0.52 mm, MLD-pre: 1.03±0.35 mm, % DS-pre: 64.75±11.81% and MLD and % DS after stent implantation was 2.47±0.46 mm and 15.47±7.17% respectively. MLD at 6M follow-up: 1.99±0.61, % DS stenosis: 32.39±15%, Late Loss: 0.48mm. Late loss was lower in the unstable angina pectoris group compared to the stable patients
Conclusion: These results show that implantation of a Biodivysio Dexamethasone eluting stent is feasible and safe. Compared to other studies, using a non drug loaded Biodivysio PC coated stent, the late loss was significantly lower, suggesting a beneficial effect on in-stent neointimal hyperplasia. This beneficial effect on late loss was more pronounced in the unstable patient group.

1456 Heparin-coated stents in small coronary arteries – Results of the COAST trial

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Background: The role of stenting compared to balloon angioplasty (PTCA) for the treatment of symptomatic coronary artery stenoses in small vessels is still unclear. In addition, the benefit of heparin-coated stents in this scenario has not been documented.
Methods: 600 patients (pts) in 21 centers with native coronary stenoses in vessels <2.6 mm were randomly assigned to one of 3 treatment arms: PTCA or non-coated JOSTENT FLEX (ST) or heparin-coated JOSTENT FLEX (H-ST) implantation. The primary endpoint was minimal lumen diameter (MLD) at 6 months. Secondary endpoints included technical success rate and eventfree survival.
Results: Based on intention to treat, 588 pts could be analyzed with a reangiography rate of 81%. Baseline parameters were similar between the 3 groups.

	PTCA	ST	H-ST	P
MLD post intervention [mm]	2.05±0.41	2.17±0.42	2.19±0.40	0.001
acute gain [mm]	1.23±0.47	1.41±0.47	1.42+/0.48	0.0001
MLD at follow-up [mm]	1.34±0.48	1.47±0.48	1.45±0.54	0.049
late loss [mm]	0.73±0.49	0.69±0.60	0.76±0.58	n. s.
net gain [mm]	0.55+/0.51	0.72±0.51	0.69+/0.59	0.047
technical success	75%	98%	98%	0.0001
restenosis rate	31%	24%	30%	n. s.
eventfree survival at 6 months	85%	89%	89%	0.189

In the PTCA group 25% of pts required cross-over to stenting because of recoil or flow limiting dissections or threatening closure, which resulted in a postinterventional "stent-like" residual diameter stenosis of 12±16%.
Conclusion: A larger postinterventional MLD and acute gain were found in the two stent groups. At follow-up, there is a borderline statistically significant MLD and net gain difference in favor of the stent groups with surprisingly similar late loss compared to PTCA. These data did not convert into statistically different restenosis rates between the three groups. Finally, the H-ST did not provide any angiographic or clinically relevant benefit over the ST in the treatment of stenoses in small native coronary arteries.

THROMBOLYSIS

1458 How does ST-segment resolution one-hour after fibrinolysis for acute myocardial infarction predict final infarct size? Insights from ASSENT 3

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Background: Little information exists regarding the relationship between early resolution of ST segment elevation and infarct size after fibrinolysis. Moreover, the relationship between early i.e. 60 minute ST resolution after initiation of TNK reperfusion and myocardial infarct size assessed by QRS score at discharge remains uncertain.
Methods: Accordingly we analyzed a subset of hospital survivors in ASSENT 3 (n=3296) who had three sequential ECGs (baseline, 60 min and discharge) free of confounders. ST segment resolution (Schroder's method) and QRS score (Selvester) were analyzed in a core ECG laboratory.
Results: The results are shown in the table - Anterior MI (n=1150) versus Non-anterior MI (n=2146). The sum of ST shift at baseline ECG are 16.4±9.0 mm for anterior MI and 10.7±6.6 mm for inferior MI (p<0.001).
Conclusion: These data demonstrate a good relationship between ST resolution at 60 minutes and QRS infarct size at hospital discharge further corroborated by the % of patients with >5x peak CK. Patients treated within two hours versus those treated >2 hours had a lower infarct size (QRS score 4.9±3.7 versus 5.3±3.8, p=0.005) further emphasizing the value of shortening time from symptom onset to reperfusion.

1459 Randomized trial comparing stenting within 24 hours of thrombolysis versus ischaemia-guided approach to thrombolysed acute myocardial infarction with ST-segment elevation

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Background: In pts with AMI and ST elevation, routine balloon angioplasty hours after thrombolysis has been strongly discouraged because of its association with a higher incidence of adverse cardiac and non-cardiac events. The GRACIA trial was designed to re-evaluate the potential benefit of an early posthrombolysis interventional approach in the era of stent and GP IIb/IIIa inhibitors.
Methods: A total of 500 patients with AMI with ST elevation were randomly assigned to 2 posthrombolysis strategies: a) angiography within 24 hours of thrombolysis (rt-PA) followed by adequate coronary revascularization with stenting or surgery, or b) a conservative approach guided by the presence of ischemia either spontaneous or provoked by non-invasive stress tests. The primary clinical end-point was the incidence of the combined event: death, AMI or the need for coronary revascularization at one- and 12-months. Revascularization of conservative patients during hospital stay was not considered as an event. This abstract summarises the evolution at 30 days
Results: Thirty percent of conservative patients underwent cardiac angiography due to recurrent ischemia or positive stress test, and 47 of them (19%) underwent revascularization before discharge. According to angiographic findings, the final treatment of interventional patients included: stenting of the culprit artery in 79%; bypass surgery in 3% and medical treatment in 16% (no significant stenosis or unsuitable anatomy). Following the protocol, abcximab was used in 27% of invasive patients. The overall mortality at 30 days was similar in both groups (conservative 2%, invasive 2.5%). The incidence of the primary endpoint at 30 days was also similar (conservative: 6%; invasive: 4.8%, p= 0.55). During hospital stay the incidence of the combined endpoint was similar in both groups (conservative: 2.4%, invasive: 4%, p= 0.31). However, the incidence of events after discharge was higher in the conservative group (3.7% vs 0.8%, p= 0.03). No differences were found in major bleeding or vascular complications (conservative 1.6%, invasive 1.6%, p= 0.73). Hospital stay was significantly shorter in the invasive group (7.6±6.4 vs 11.2±6.8 days, p= 0.0001).
Conclusions: Early posthrombolysis catheterisation and appropriate intervention (stenting or surgery) is a safe strategy that: 1) does not increase events (cardiac, vascular or bleeding complications); 2) reduces hospital stay and; 3) reduces post-discharge incidence of events.

1460 Biochemical predictors of thrombolysis effectiveness early in the course of ST-segment elevation myocardial infarction

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Background: Rapid and adequate reperfusion of the jeopardized myocardium is the only effective treatment in the patients with ST-segment elevation myocardial infarction (STEMI). Whilst the benefit of thrombolysis is unequivocal, reperfusion fails in many patients. The aim of this prospective study was to evaluate the role of the plasma levels of either high sensitivity C-reactive protein (hs-CRP), cardiac troponin I (cTnI), or fibrinogen on the thrombolysis effectiveness estimating by continuous 12-lead electrocardiographic analysis (12L-ECG).
Methods: To examine the time course of ST segment recovery during the administration of intravenous thrombolysis a total of 157 consecutive patients with STEMI were studied. All pts had presented in the first 6 hours from onset of index pain. The course of higher ST-segment elevation was evaluated by continuous 12L-ECG monitoring. Successful thrombolysis was considered as the abrupt 50% ST-segment stable recovery in the first 90 minutes after thrombolysis initiation. Plasma levels of the studied markers were estimated upon admission.
Results: Seventy-nine patients had positive (>0.1ng/Lt) cTnI. There was a significant relationship between plasma cTnI values and prehospital delay (time interval from index pain to admission)(Spearman R=0.51; p<0.001). Patients with or without positive cTnI didn't differ significantly concerning the mean values of either hs-CRP (0.58mg/dl vs.0.54mg/dl respectively; p=0.65) or fibrinogen (3.4g/Lt vs.3.3g/Lt respectively; p=0.85). In the first 90 min 85 (85/157; 54.1%) patients had attained 50% ST-segment recovery. By univariate logistic regression analysis cTnI (RR=0.44; p=0.001), time interval from index pain to thrombolysis initiation (RR=0.68; p<0.001), hs-CRP (RR=0.74; p<0.001), and diabetes mellitus (RR=0.27; p=0.001) were related to thrombolysis effectiveness. Fibrinogen was not related to thrombolysis effectiveness (RR=0.93; p=0.54). However, by multivariate analysis time interval from index pain to thrombolysis initiation (RR=0.54; p<0.001), hs-CRP (RR=0.66; p=0.01), and diabetes mellitus (RR=0.30; p=0.009) were the only independent predictors of thrombolysis outcome.
Conclusions: The present study implies that hs-CRP is a strong predictors of thrombolysis effectiveness whilst elevated plasma cTnI values may reflect the preceding myocardial necrosis (strong association with prehospital delay). Fibrinogen is not associated with thrombolysis outcome. Acute inflammatory reaction at the culprit artery may be responsible for the fail of thrombolysis in patients with high CRP values.

Abstract 1458 – Table: Anterior MI versus Non-anterior MI

ST resolution at 60 min	Anterior MI >70%	Anterior MI 30-70%	Anterior MI <30%	Non-ant MI >70%	Non-ant MI 30-70%	Non-ant MI <30%
No of pts	299	401	450	829	663	654
Peak CK >5 uln	54.9	75.2	82.4*	48.8	(68.8)	(71.5)*
QRS score at D/C	4.7±3.3	6.2±3.5	6.8±3.5*	4.2±3.5	4.8±3.8	5.4±3.9*
Treated <2hr	3.8±2.9	5.8±3.5	6.9±3.5*	(3.9±3.4)	(4.4±3.7)	5.2±3.9*
Treated >2hr	5.2±3.4	(6.4±3.6)	(6.8±3.5)*	4.3±3.6	4.9±3.8	5.4±3.9*

*p<=0.031 for all pair-wise comparisons across 3 categories of ST resolution except pairs in brackets

1461 Effect of tenecteplase versus alteplase on platelets in patients during the first three hours after acute myocardial infarction

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Background: Platelets play a pivotal role in the pathogenesis of acute myocardial infarction (AMI), as well as in coronary artery reocclusion and occurrence of bleeding events. Ultimately, the success of certain fibrinolytic agents is highly dependable on their direct effects on platelets. We sought to determine how tenecteplase (TNK) and alteplase (t-PA) affect platelets in vitro as in a setting of an ASSENT-2 clinical trial.
Methods: For the in vitro study, whole blood of donors was incubated with 30 mg TNK and 60 mg t-PA. Platelet aggregation, bedside analyzers, and flow cytometry measuring 9 major receptors and platelet-monocyte microparticles were utilized. Forty-one patients (21-TNK, and 20-t-PA) from a single ASSENT-2 site underwent 7 serial sampling of plasma every 30 minutes for 3 hours. Levels of PECAM-1, VCAM-1, P-selectin, beta-thromboglobulin, platelet factor 4, thromboxane, and prostacyclin were measured by ELISA.
Results: Significant inhibition of conventional and whole blood platelet aggregation, decreased platelet activation by Ultegra, and prolonged closure time with the PFA-100 device were observed in the TNK treated samples. Flow cytometry reveals decreased expression of GP IIb/IIIa, PECAM-1, vitronectin receptor, CD151, and formation of the platelet-monocyte microparticles after incubation with TNK. Assessment of serial samples in the ASSENT-2 trial showed a significant decrease of soluble platelet-endothelial biomarkers in the TNK group. There was a trend toward decreased platelet function with t-PA; however, these differences were much smaller than those observed with TNK.
Conclusion: Both in vitro and ex vivo studies show that t-PA and TNK affect platelet function in human volunteers and in patients with AMI early after thrombolysis. Comparison between agents revealed that anti-platelet properties of TNK are much stronger than those of t-PA. These data challenge simultaneous use of fibrinolytic agents and platelet GPIIb/IIIa inhibitors.

1462 Bolus intravenous heparin as reperfusion therapy for acute myocardial infarction

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Introduction: Early reperfusion of infarct related coronary artery has been reported to be associated with improved prognosis in acute myocardial infarction (AMI). We sought the effect of early administration of bolus intravenous heparin on reperfusion in AMI.
Methods: Eighty-nine patients with AMI presenting within 6 hours after onset were randomized to 3 groups (150U/kg heparin bolus at arrival at emergency department, 75U/kg heparin at arrival, or 75U/kg heparin at the beginning of emergent coronary angiography). No other thrombolytic agents were given. Patients with cardiogenic shock were excluded. Patency of infarct related artery was assessed by emergent coronary angiography with TIMI grade. After TIMI flow grade evaluation, coronary angioplasty or stenting was performed on indication.
Results: There were no differences in age, sex, time from onset of AMI to arrival, or Killip functional class among the 3 groups. Time from administration of heparin to initial angiography was 44±11 minutes in patients with heparin at arrival and 3±2 minutes in patients with heparin at angiography. TIMI 2 or 3 flow was more often seen in patients with 150U/kg heparin at arrival (13 of 29 patients: 45%) or 75U/kg heparin at arrival (12 of 30 patients: 40%) than in patients with 75U/kg heparin at angiography (5 of 30 patients: 17%)($p<0.05$). In each group, 1 patient showed ventricular fibrillation between arrival and angiography. There were no in-hospital deaths. One patient with 75U/kg heparin at arrival showed massive gastric bleeding. No other serious bleeding was seen.

Number of patients with each TIMI grade

	Heparin 150U/kg at arrival (n=29)	Heparin 75U/kg at arrival (n=30)	Heparin 75U/kg at angiography (n=30)
TIMI 0	12	16	22
TIMI 1	4	2	3
TIMI 2	8	6	3
TIMI 3	5	6	2

Conclusions: Bolus heparin given at arrival at hospital showed increased rate of coronary reperfusion without increasing serious complications. Utilization of this inexpensive and easily applicable therapy should be considered in AMI.

1463 Pre-hospital thrombolysis reduces incidence of ischaemic heart failure after acute myocardial infarction

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Background: Randomized trials comparing primary angioplasty and in-hospital thrombolysis in acute myocardial infarction (AMI) have shown an advantage for primary angioplasty on left ventricular ejection fraction (LVEF). The pre-hospital thrombolysis with a mean gain of one hour compared with in-hospital thrombolysis could improve LVEF as well as primary angioplasty for AMI. This study compares the benefits on LVEF and in-hospital outcome after pre-hospital thrombolysis versus primary angioplasty in patients with acute myocardial infarction (AMI).
Methods: We conducted a study including 318 patients with AMI hospitalized in a single center from 1995 to 1999. Patients underwent primary angioplasty (primary PTCA group: n = 157) or received pre-hospital thrombolysis with accelerated rtPA (pre-hospital thrombolysis group: n = 161) within 6 hours after the onset of chest pain. We noted the LVEF and looked at the in-hospital outcome focusing on global mortality and major adverse cardiac events (MACE).
Results: The two groups were similar in their baseline characteristics. No difference was noted between the 2 groups for LVEF (52.3 ± 9.7% for primary PTCA group versus 51.8 ± 11.4% for pre-hospital thrombolysis group; p = 0.98) at the hospital discharge. No difference was noted for in-hospital mortality (primary PTCA group: 2.48%, pre-hospital thrombolysis group: 2.54%) with no increased risk of major bleeding event (primary PTCA group 1.91% versus pre-hospital thrombolysis group: 2.48%; p = 0.72). Regarding MACE (primary PTCA group: 10.8% vs. pre-hospital thrombolysis group: 7.45%; p = 0.29), the groups were statistically not different.
Conclusion: Pre-hospital thrombolysis prevent ischaemic heart failure after AMI as well as primary angioplasty. We could reduce the incidence of ischaemic heart failure after acute myocardial infarction by early initiation of reperfusion therapy with pre-hospital thrombolysis. Consequently our results in the real-life world encourage more frequent use of thrombolytic therapy in the pre-hospital stage.

NEW DEVICES FOR INTERVENTIONS IN ACUTE MYOCARDIAL INFARCTION

1464 Thrombo-aspiration with the "Rescue" system in acute myocardial infarction. Comparison of immediate results between rescue use and primary use

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Purpose: Thromboaspiration (TA) with the "RESCUE" system (Boston Scientific) seems to be a logical treatment in Acute Myocardial Infarction (AMI) in case of thrombotic occlusion. It can be used as a primary therapy (primary TA) or after failure of reperfusion post angioplasty (rescue TA). We compared the immediate angiographic and ECG results between the two strategies.
Methods: Non randomized, single center registry. Immediate results were assessed by the TIMI flow, ST elevation changes and absolute value, Creatine Kinase (CK) and troponin TI release at 24 hours. All patients were pre treated by enoxaparin (1mg/kg), 2b/3a inhibitors and aspirin (250 mg).
Results: Of the 30 consecutive patients (64±13 years) entered in the registry, AMI was anterior in 9, lateral in 5 and inferior in 16. TA was used as rescue in 15 (50%) and as primary in 15(50%), without additional angioplasty in 8(27%). TIMI flow was 0 in all patients before procedure and afterwards was 3 in 19 patients (63%), 2 in 7 (23%); while 4 had no successful reperfusion (13%). The comparison of the results between primary and rescue strategy is presented in the table.

	TIMI3 flow post	ST elevation pre (mm)	ST elevation post (mm)	Changes in ST elevation	CK at 24h (U/l)	Troponin at 24h
Primary TA	10/15	4.1±2.0	1.2±1.5	2.9±0.6	1023±662	27±32
Rescue TA	9/15	4.9±1.7	2.2±1.7	2.7±0.5	2241±1102	54±33
P value	0.70	0.13	0.12	0.75	0.002	0.045

Conclusions: TA using the "RESCUE" system can be used as a primary therapy as well after failure of reperfusion with balloon angioplasty. Enzyme release seems lower when used as primary choice.

1465 Use of a porous filter protection system during direct angioplasty on native coronary arteries

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The benefits of vessel recanalization induced by primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) are limited by the possibility to induce distal embolization of the fresh thrombus or plaque which in turn may be related to the appearance of the no-reflow phenomenon. Aim of this study was to evaluate the safety and feasibility of the use of the "Filter-wire Ex" (FW), a distal embolic protection device, during primary PCI on native coronary vessels. Methods: 23 consecutive patients (18M,5F, age 62±9 yrs) admitted < 6 hours after AMI onset and with TIMI grade flow 0 or 1 in the infarct native coronary vessel were treated by primary PCI in association with FW to prevent distal embolism. Hospital outcome of these patients (group PCI+FW) was compared to 23 patients with AMI treated by primary PCI alone (group PCI) matched for age, sex and infarct location. Patients with cardiogenic shock, left main coronary artery disease or infarct vessel size < 3.0 mm were excluded. Results: successful positioning of the FW device was obtained in 22 out of 23 patients while visible emboli in its basket were recovered in 7 patients. Demographic and baseline clinical characteristics were similar in the two groups with the exception of the arterial puncture-to-vessel recanalization time, slightly longer in the PCI+FW group (24±6 vs 21±5 min, p<0.05). The prevalence of persistent ST-segment elevation (pSTe) and TIMI grade flow 0-2 at the end of PCI as well as a composite end-point (CEP) at 4 weeks including death, heart failure, recurrent angina or AMI were higher in the PCI group with respect to the PCI+FW group (see table). Improvement of the 2D-echo left ventricular regional wall motion index (delta-RWMI) 4 weeks after AMI was significantly greater in the PCI+FW group (see table).

	TIMI 0-2 after PCI	pSTe	CEP	delta-RWMI
PCI	22%	35%	39%	-0.25±0.26
PCI + FW	4%	9% *	13%*	-0.41±0.21*

*: p<0.05

Conclusions: the use of the FW device during primary PCI in patients with AMI is safe and technically feasible in native coronary arteries. In this clinical setting, FW seems to prevent the no/slow-reflow phenomenon improving the recovery of the left ventricular wall motion.

1466 Primary angioplasty with thrombectomy devices. Experience at one centre

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As Primary Angioplasty (PA) is performed in lesions with large thrombus burden, it is associated with an increased risk of acute occlusion, distal embolization and no-reflow. Thrombectomy devices (TD) may avoid this complications and lead to a better procedure outcome. Our aim was to analyse the efficacy of thrombus extraction with TD during PA.

Methods: Retrospective analysis of PA performed with TD to patients with AMI at our hospital. Two devices were used: XSizer 4.5 and 6 F (Endicor Medical) and Rescue (Scimed).

Results: Twenty-three patients were treated with PA and TD (age 63±11.2, 66% male), 17.3% of them in cardiogenic shock. XSizer was used in 7 (30.4%) and Rescue in 16 (69.6%), with an 8 (21.8%) or 7 French (78.2%) guiding catheter. All patients received stent and abciximab was administered in 69.5%. Culprit vessel was RCA in 16 (69.5%), LDA in 6 (26.1%) and saphenous vein graft in one case. The artery was occluded in 20 patients (87%) and TIMI flow during different stages of the procedure is shown in the table.

	Initial	After guidewire	After Thrombectomy device	Final Result
TIMI 0	20 (87%)	1 (4.3%)	1 (4.3%)	1 (4.3%)
TIMI I	3 (13%)	15 (66.2%)	0	0
TIMI II	0	6 (26.2%)	8 (34.8%)	0
TIMI III	0	1 (4.3%)	14 (60.9%)	22 (95.7%)

TIMI flow during the procedure.

Once the guidewire crossed the stenosis, intracoronary thrombus was seen in all cases; after TD usage, thrombus image disappeared in 8 cases (36.4%), improved clearly in 6 (27.3%) and slightly in 3 (13.6%), with no changes in one (4.5%).

After PA, final flow was TIMI III in 22 patients, myocardial perfusion was blush grade 3 in 12 (54.6%), 2 in 9 (39.1%) and 1 in one patient (4.5%).One patient with shock at admission died during the procedure.

Conclusion: Thrombectomy devices during primary PTCA are associated with efficient thrombus extraction, achieving a good angiographic result and leading to high procedural success.

1467 More rapid ST-segment resolution and improved epicardial flow using the embolisation protection device GuardWire in percutaneous coronary intervention for acute myocardial infarction

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Background: Percutaneous coronary interventions (PCI) in acute myocardial infarction (AMI) are associated with high success rates. However, high epicardial flow grades alone do not indicate adequate myocardial reperfusion as demonstrated by delayed or absent ST-segment resolution (ST-RES) and/or low tissue level (re-)perfusion (TIMI myocardial perfusion grade =TMPG) in a substantial proportion of patients (pts). Possibly, embolic debris liberated in excess during PCI are responsible for this observation. We speculated that the embolisation protection device GuardWire (GW) might reduce the embolic burden during PCI and thus improve these reperfusion parameters.

Methods: A total of 55 pts with complete occlusion of the infarct related artery and ST-elevation underwent PCI for AMI (<12 hours from symptom onset) using either conventional (n=30 pts) or GW-assisted (n=25 pts) PCI. Pre/post-PCI core lab analysis compared TIMI flow grades (TFG), corrected TIMI frame counts (CTFC), TMPG and ST-RES between the groups.

Results: Clinical and baseline angiographic data in GW and non-GW pts were identical (except for a lower number of LAD in the GW group). Post-PCI, GW pts had much better TFG 3 (100% vs. 75%, p<.008), CTFC (20.0±5.4 vs. 44.0±30.3, p<.009) and ST-RES (77.4±17.3% vs. 50.0±26.2%, p<.0001) while TMPG 3 improved alike in both groups (40% vs. 50%, p=.50).

Conclusions: In this first comparative study, reperfusion seems improved with distal embolisation protection in PCI for AMI. Larger trial are needed to confirm these preliminary observations and to assess its clinical benefits.

1468 Postinfarct VSD closure with amplatzer atrial septal occluders

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Background: Amplatzer Atrial Septal Occluders (ASO) were applied rutinely in our center to close ASD II The unique construction of ASO also permits to close others undesirable shunts, which is sometimes a life saving procedure. Experience in transcatheter treatment of postinfarct VSD with ASO is presented.

Patients & methods: Five patiens (pts) with mean age 61 (from 51 to 71) years were included. The procedure was performed between 1.5 and 12 months (mean 4.5 m) after myocardial infarction. One pt had double VSD (residual post 2 months earlier surgery) and another coexisting critical stenosis of right coronary artery. All pts were in III/IV NYHA class. In all venous jugular approach was applied to close VSD.

Results: All procedures, but one were finished successfully. In one pt cannulation of VSD appeared impossible both from venous and arterial side, because of its oblique intraseptal trajectory (which was confirmed during subsequent operation). In 4 pts post infarct VSD's were closed with 5 ASO (in postsurgical pt 2 ASO were apllied) and immediate significant clinical improvement was achieved. In one pt prior to VSD closure, PTCA and stent implantation of RCA was performed. The stretched diameter of VSD ranged from 15 to 19 (mean 17) mm.and the size of implanted devices from 16 to 20 (mean 18) mm. Fluoroscopy time was 45 (18-87) min. During procedure ventricular fibrillation requiring defibrillation was frequent. One pt died one week after procedure because of multiorgan failure and increasing mitral incompetence.

Conclusions: Implantation of Amplatzer occluders, despite some technical problems, is an atrractive option of tratment for patients with postinfatct VSD.

1469 Thrombectomy prior to stenting is a novel strategy to obtain optimal reperfusion in acute myocardial infarction patients

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Background: A goal of reperfusion therapy is to obtain TIMI 3 flow at both epicardial and myocardial perfusion. The purpose of this study was to evaluate the efficacy of thrombectomy prior to stenting for the myocardial optimal perfusion. Objects and Method: A consecutive 92 acute myocardial infarction patients underwent primary angioplasty were studied. Subjects were divided into 2 groups by means of the use of RescueTM thrombectomy catheter (Rescue group: 40 cases, non Rescue group: 52 cases). To evaluate epicardial and myocardial reperfusion after primary angioplasty, ST-segment elevation were measured from twelve-lead electrocardiograms before angioplasty and 1hr after reperfusion, and the sum of the ST-segment elevation and ST-segment resolution was calculated. ST-segment resolution was classified into 3 groups: complete (>70%), partial (30% to 70%), non (<30%), and we evaluated the percentages of ST-segment resolution 1hr after angioplasty.
Results: There is no difference in the baseline characteristics of both groups, including elapsed time, using tPA and TIMI grade before PTCA. The data of electrocardiographic analysis was as follows.

The data of ST-segment resolution

	Rescue (n=40)	non Rescue (n=52)	p value
Sum of ST-segment elevation before angioplasty(mV)	0.97±0.85	0.93±0.98	NS
ST-segment resolution 1hr after angioplasty(%)	62.1±22.9	29.6±29.4	<0.0001
complete, n(%)	19 (47.5)	6 (11.5)	0.001
partial, n(%)	20 (50)	18 (34.6)	NS
non, n(%)	1 (2.5)	28 (53.9)	<0.0001

Conclusions: Thrombectomy with RescueTM prior to stenting is associated with early and greater ST-segment resolution. These findings may suggest that thrombectomy before PTCA is a useful strategy for obtaining sufficient epicardial and myocardial reperfusion.

BNP IN HEART FAILURE: PREDICTORS OF OUTCOME

1470 The prognostic significance of NT-proBNP in severe chronic heart failure is independent of aetiology: a substudy of the COPERNICUS trial

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Background: Recently, prognostic significance of the new cardiac marker N-terminal proBNP (NT-proBNP) was documented in ischemic cardiomyopathy (CMP). The COPERNICUS study offered the unique possibility to evaluate the value of NT-proBNP to predict the occurrence of death and hospitalisation in patients with severe congestive heart failure of different aetiology.
Methods and Results: Baseline plasma concentrations of NT-proBNP were measured using a newly developed sandwich ELISA in a subgroup of 695 patients with ischemic and 353 patients with non-ischemic CMP having symptoms at rest or on minimal exertion who were enrolled in the European part of the COPERNICUS study and were randomised to placebo (n=524) or carvedilol (n=524) for up to 29 months. NT-proBNP concentrations were markedly increased (mean ± SD = 579 ± 822 pmol/L), with significantly higher levels in the ischemic CMP patients (624 ± 862 vs. 491 ± 732 pmol/L). By univariate and multivariate Cox regression, NT-proBNP (analysed as a continuous or categorical variable) was found to be a powerful predictor of all cause mortality (see table) and other major clinical events, all p < 0.0001. Predictive value of NT-proBNP was similar when both patients with ischemic and non-ischemic CMP were analysed separately, no statistically significant interaction was detected between NT-proBNP and aetiology (p=0.5 for NT-proBNP classification by median).

One-year mortality rates

	NT-proBNP		Risk Ratio	95% CI
	< median	> median		
All patients (n=1048)	6.2%	22.4%	3.13	1.94 - 5.07
Ischemic CMP (n=695)	8.6%	25.0%	2.70	1.56 - 4.70
Non-ischemic CMP (n=353)	3.1%	18.2%	4.60	1.70 - 12.49

Conclusion: Circulating levels of NT-proBNP predict all cause mortality and major clinical events in patients with severe heart failure, independent of aetiology of CMP.

1471 Association between N-terminal pro brain natriuretic peptide and left ventricular function in mild to moderate heart failure

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Background: N-terminal pro brain natriuretic peptide (NT-proBNP) has been reported to be a useful marker in the diagnosis of chronic heart failure (CHF). However, the diagnostic value of the marker in patients with mild to moderate CHF has not been well characterized, and even more importantly, only little is known about possible confounders for interpretation of a given NT-proBNP concentration in the individual patient. The aims of the present analysis from the Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation (CARMEN) trial were (I) to evaluate NT-proBNP as a marker for left-ventricular (LV) dimensions and systolic function, and (II) to identify variables of independent significance for the plasma level of NT-proBNP in a large group of patients with mild to moderate CHF.
Methods: At baseline, 504 patients (406 men, 98 women) (mean (SD) age=62.4 (11.4) years) with LV systolic CHF (LV ejection fraction (LVEF) < 39%; mean (SD)=29.2 (6.48)%) in NYHA classes I - III (I:28 (6%), II:332 (66%), III:144 (29%)) were examined clinically, and echocardiograms (n=408, by central core-lab) and blood samples (NT-proBNP by non-extracted, enzyme-linked, sandwich immunoassay) were obtained.
Results: (log) NT-proBNP (geometric mean (95% CI)=150 (136-165) pmol/l) was significantly associated with LVEF (r=-0.49, p<0.0001), and LV end-diastolic (mean (SD)=87.8 (25.5) ml/m^2; r=0.40, p<0.0001) and end-systolic (mean (SD)=63.2 (22.9) ml/m^2; r=0.45, p<0.0001) volume indices. By multiple linear regression analysis, low LVEF (standardized parameter estimate (SPE)=0.44, p=0.002), high age (SPE=0.26, p<0.0001), high NYHA class (SPE=0.17, p=0.0001), high heart rate (mean (SD)=77.7 (11.3) bpm; SPE=0.15, p=0.0003), high serum creatinine (mean (SD)=105 (23.9) μmol/l; SPE=0.15, p=0.0009) and low diastolic blood pressure (mean (SD)=80.8 (10.1) mmHg; SPE=0.13, p=0.02) were all independently associated with a high plasma level of NT-proBNP.
Conclusion: NT-proBNP is strongly associated with LV dimensions and systolic function in patients with mild to moderate CHF. When interpreting a given value of NT-proBNP, it may be necessary to adjust for the independent effects of age and renal function.

1472 Changes in plasma brain natriuretic peptide and norepinephrine over time and subsequent mortality and morbidity in Val-HeFT

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Background: Plasma brain natriuretic peptide (BNP) and norepinephrine (NE) are important determinants of the progression of heart failure (HF) and predict long-term mortality and morbidity (M&M). Whether changes in BNP and NE over time correspond to subsequent changes in M&M has not been studied. The Val-HeFT trial that evaluated the efficacy of valsartan in 5010 patients with NYHA class II to IV HF, and measured BNP and NE at baseline and sequentially during follow-up provided an opportunity to examine this relationship. Methods: Baseline (BL), and the % change from BL to 4 months in BNP (n=3740) and NE (n=3746) were analysed by quartiles (Q) for subsequent mortality (Mort), and first morbid event (Morb: death, sudden death with resuscitation, IV inotropic therapy, and hospitalisation for HF), using a Cox proportional hazard model with baseline values as a covariate. The hazard risk ratio (RR) and 95% CI for changes between quartiles, using first Q as control was calculated for mortality and first morbid event, in all patients irrespective of treatment group. P-values were computed using log-rank test.

Table

Quartiles		% Mort	RR vs Q1	95% CI	Log Rank P-value	% Morb.	RR vs Q1	95% CI	Log Rank P-value
	% Change in BNP								
Q1	<-45	13.6	1.00			21.5	1.0		
Q2	-45 to -13	15.5	1.30	1.03-1.66	0.165	25.5	1.37	1.33-1.65	0.027
Q3	-13 to +30	15.1	1.36	1.07-1.74	0.321	28.1	1.65	1.37-2.00	0.0009
Q4	≥ +30	19.1	1.92	1.52-2.43	0.0006	33.0	2.24	1.86-2.69	<0.0001
	% Change in NE								
Q1	<-24	14.4	1.00			25.9	1.00		
Q2	-24 to+4.5	16.0	1.23	0.97-1.55	0.30	26.3	1.12	0.93-1.33	0.82
Q3	+4.5 to+41	15.7	1.28	1.01-1.62	0.30	27.4	1.24	1.04-1.48	0.27
Q4	≥ +41	17.5	1.48	1.17-1.87	0.066	29.2	1.41	1.18-1.68	0.05

Results: Baseline BNP and NE in quartiles showed a significant quartile-dependent increase in M&M. Patients with the greatest decrease in BNP at 4 months (Q1) had the lowest subsequent M&M. RR for subsequent M&M increased significantly in patients with smaller decreases or increases in BNP (Q2 to Q4) over time (table). Similar findings were seen for NE, although the results did not reach a level of significance. Conclusions: Both BL and % changes in BNP over time are related to subsequent events.

1473 NT-pro BNP predicts toleration of beta-blocker therapy in patients with chronic heart failure

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Recently, the results of several studies have provided convincing evidence that beta-blockers (BB) decrease mortality in patients with symptomatic chronic heart failure (CHF). However, extensive surveys carried out in Europe indicate the use of BB in clinical practice is still very low (between 9% and 52%) and only 21% in the UK. This is partly due to difficulties in implementation of this treatment and reluctance to commence therapy in the community. The aim of this study was to examine implementation of BB therapy in a dedicated CHF clinic and to assess the possible use of NT-pro BNP to predict toleration of beta-blocker therapy.

All patients (86) referred from the CHF clinic for commencement of BB therapy from 01/10/1999 to 01/10/2001 were included. Data was collected detailing aetiology of CHF, co-morbidity and concurrent drug therapy as well as LV function from the initial echocardiogram. At the first visit the lowest licensed dose of BB was started and doubled every 2 weeks until maximum dose was achieved. Patients were observed for 3 hours each visit, and pulse and blood pressure were recorded every 30 minutes. Side-effect profile was recorded, as well as follow up data on drug compliance. NT-pro BNP was measured at initial visit to the clinic and on average every 3 months thereafter during uptitration of BB.

Data was available on 86 patients. Average age was 67 (range 23-86 years of age). Of the patients referred 48.7% had severe LVD, 48.7% moderate LVD and 6.3% mild LVD. NYHA was also graded; 17.9% were grade I, 46.4% grade II, 28.6% grade III and 7.1% grade IV. 89.5% patients tolerated BB therapy with 41.9% established on full dose therapy. Average time taken to establish the patient on their maximum tolerated dose was 10 weeks (range 8-44 weeks). Multivariate analysis was performed using multiple linear regression. The only significant, independent, predictors of toleration of BB therapy were NT-pro BNP level before commencement of BB and during uptitration of BB. The higher the NT-pro BNP level, the less likely the patient was to tolerate BB therapy. A history of COPD or PVD did not predict toleration of BB and nor did NYHA class or echocardiographic findings of severe LVD.

BB therapy can be safely and effectively commenced in the majority of patients with CHF. NT-pro BNP predicts which patients will tolerate full dose BB therapy and could therefore be of use in the future to determine which patients with CHF could safely be commenced and uptitrated on BB in the community rather than attending hospital supervised programmes.

1474 Pre-discharge but not admission levels of NT-proBNP independently predict death and heart failure after admission with acute heart failure

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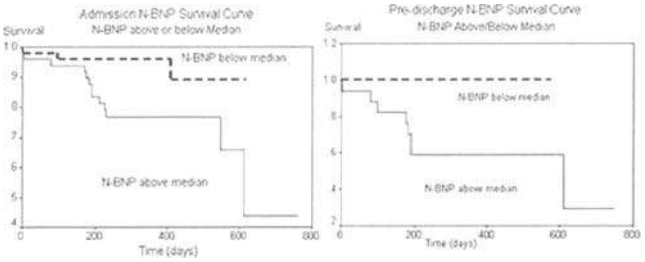
Plasma N-terminal pro B-type natriuretic peptide (N-BNP) reflects LV function and prognosis in heart failure. We studied its correlation with measures of LV function during admission with LVF ± unstable angina (UA), and its utility in predicting death, further LVF and other endpoints. Admission plasma N-BNP was measured in 96 unselected patients (mean age 74, range 46-93) with acute LVF (LVF alone=61, LVF with UA =35) and before discharge in 36. Median N-BNP was 2944 pM on admission (14-29368) and 1944 pM (14-8155) pre-discharge. It rose proportionally to degree of LV dysfunction on echo (p=0.001). N-BNP correlated with age (p=0.0005), 1/Creatinine (p=0.0005) and rose with increasing peak Killip class (p=0.0005). There was no correlation of N-BNP with history of previous MI, hypertension, diabetes, hyperlipidaemia, or angina. During median follow-up of 350 days (range 2-762) 15 (16.7%) patients died, 21 (21.8%) were readmitted with LVF, and 15(15.7%) were hospitalised with UA. A further 17 (17.7%) had clinical LVF at outpatient visit. No episode of non-fatal MI was recorded. N-BNP was higher in those who died (5663.7 v 1631.9 pM, p=0.013), were readmitted with LVF (p=0.04), had outpatient LVF (p=0.049), or a composite of these (p<0.001). N-BNP on admission or discharge above the median was associated with reduced survival (Fig 1,log ranks p=0.015 and p=0.003 respectively).



However, only pre-discharge N-BNP was independently predictive of a composite of mortality and heart failure in multivariate analysis (odds ratio 15.30 [1.4-168.9],p=0.026).No deaths occurred in patients with pre-discharge N-BNP below median. N-BNP is dramatically raised in acute LVF.Pre-discharge rather than admission levels may be more representative of long-term prognosis.

1475 N-terminal BNP in the community diagnosis of suspected heart failure: what is an appropriate diagnostic threshold?

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Background: Brain natriuretic peptide (BNP) is potentially useful for the diagnosis of suspected heart failure (HF) presenting in the community. However, patients with suspected HF are often elderly with other medical conditions that can elevate BNP, causing false positives. Normal ranges for BNP are often established in populations of healthy subjects considerably younger than symptomatic patients presenting in primary care.
Methods: Patients with dyspnoea and/or oedema presenting to their general practitioners (GPs) were entered into a randomised, controlled effectiveness trial of BNP (the Natriuretic Peptides in the Community Study). Each patient underwent full clinical assessment including ECG, chest x-ray, echocardiography and N-terminal BNP measurement (normal range of 0 to 50 pmol/l) by an independent study investigator. An independent expert panel decided whether or not HF was present using ESC criteria.
Results: 304 patients were included, mean age 72 yrs (SD 11.4), 65% female. 77 patients (25%) met the case definition for HF; these patients had a significantly higher N-terminal BNP than those without HF, 286 (SD 319) vs 61 (SD 67) pmol/l, p=0.0001. The frequentist parameters for BNP in the diagnosis of HF are shown in the table.

Frequentist parameters for BNP

Nt-BNP, pmol/l	Sens, %	Spec, %	PPV, %	NPV, %
>50	89	62	49	94
>100	59	91	75	82
>150	56	93	78	84

From the receiver operating characteristic curve (ROC) for BNP, the diagnostic threshold providing optimal sensitivity and specificity for the diagnosis of HF was 125 pmol/l. The area under the ROC curve for BNP was 0.82.
Conclusion: For a cohort of elderly patients presenting to GPs with symptoms suggestive of heart failure, the diagnostic threshold for N-terminal BNP with optimal sensitivity and specificity was 125 pmol/l. For clinical use in the community, a recommended BNP diagnostic threshold between 100 and 150 pmol/l is appropriate in terms of a high specificity and negative predictive value. The diagnostic threshold for BNP should be carefully considered in the population in which the test is utilised, and may be very different from the upper range of normal.

DETERMINANTS OF LONG-TERM PROGNOSIS IN HEART FAILURE

1476 The efficacy of new interventional programmes depends on the stage of heart failure, evaluated by BNP plasma concentration

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Background: Interventional programmes, including heart failure (HF) outpatient clinics and HF nurse specialists improve life quality, reduce readmission rates and decrease costs.Little is known in which stage of disease such interventions are most effective. Therefore we evaluated the impact of severity of HF, determined by BNP plasma levels, on the efficacy of special outpatient care ("SOPC") in comparison with conventional outpatient care ("COPC"). Methods:112 HF patients (mean age: 68±12 years, 63% males) who were hospitalized 3 months prior to study entrance were randomized to SOPC (n=48) or COPC (n=64). In all patients an individual prescription of RAAS antagonists and additional betablockade including an uptitration schedule according to the ESC guidelines was performed by a cardiologist at the first visit in the HF outpatient clinic. Diuretic regimens and additional therapies (digitalis, anticoagulants, antiarrhythmics) were prescribed as clinical appropriate. In the SOPC group regular home visits by a nurse specialist were arranged after 3,6 and 12 months as well as in case of worsening HF to controll the precribed therapeutic regimen, body weight, heart rate, blood pressure and signs and symptoms of HF.Results: In the SOPC group a significant reduction of the event rate (readmission rate and all cause mortality) was achieved (17% vs. 33%; p=0.04). BNP plasma levels were comparable in both groups (314±272 vs. 369±369 pg/ml; p=n.s.). Patients with BNP values <260 pg/ml had a comparable 1 year event-rate, with and without SOPC (0% vs. 3%; p=n.s.). Patients with BNP values >260 pg/ml, treated with SOPC had more events compared to patients with BNP values <260 pg/ml treated with COPC (32% vs. 3%; p=0.002). Patients with BNP values >260 pg/ml had fever events with SOPC than with COPC (32% vs. 75%; p=0.003). Conclusion: The efficacy of SOPC depends on the severity of disease evaluated by BNP levels. BNP determination might be helpful in selecting patients for novel care programmes, especially when resources are limited.

1477 Prognosis and heart failure: role of C-reactive protein?

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Background: Clinical studies suggest that inflammation with activation of the cytokine pathway is important in chronic heart failure (CHF) and may be responsible for an adverse outcome in these patients (pts). Thus, the present study evaluates C-reactive protein (CRP) values in CHF pts with regard to severity of the disease and mortality.
Patients and methods: Laboratory evaluation including CRP (norm < 5 mg/l) echocardiography and/or cardiac catheterization were carried out in 126 pts (84% males) with CHF. NYHA-classification was assessed in all pts. Secondary reasons for CRP elevation (infections, tumors, chronic inflammatory diseases) were excluded. Mean age was 54 ± 12 years. 44% pts had coronary artery disease, 51% dilated cardiomyopathy, and 5% valvular heart disease. Mean follow-up was 2.3 ± 1.8 years. Independent predictors for mortality were determined in a stepwise logistic regression model. For mortality analysis, transplanted pts were excluded.
Results: 8% of all pts were in NYHA-class I, 29% in NYHA II, 46% in NYHA III, and 17% in NYHA IV. During follow-up 15 pts (12%) died and 52 pts (41%) were transplanted. CRP values (mean ± SEM, mg/l) in the 4 NYHA-classes were as follows: NYHA I = 2.5 ± 0.4, NYHA II = 3.9 ± 0.6[1], NYHA III = 8.8 ± 1.5[2], and NYHA IV = 9.3 ± 3.3[2], [1]p<0.05 vs. NYHA I,[2]p<0.001 vs. NYHA I. Survivors had a mean CRP level of 3.9 mg/l, pts who were subsequently transplanted 6.2 mg/l, and pts who died during follow-up 21.6 mg/l (p<0.001). 93% of all survivors had a CRP < 7.5 mg/l, whereas 74% of all pts who died had a CRP > 7.5 mg/l. The predictive value of a CRP > 7.5 mg to die during follow-up was 75%. CRP, age and left ventricular ejection fraction were independent predictors for mortality (p<0.01), but not NYHA-class and gender (p>0.5).
Conclusions: CRP is an independent predictor for mortality and is significantly related to the severity of CHF. Furthermore, it allows to identify pts with an increased mortality. Thus, CRP is an simple and reliable parameter for assessing clinical outcome in pts with CHF.

1478 Comparative prognostic significance of plasma aldosterone, BNP, norepinephrine and renin in 4305 patients with heart failure in Val-HeFT

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Background: Elevated plasma concentrations of several neurohormones (NH) are related to increased mortality/morbidity in patients with heart failure (HF). In most previous studies, the size of the sample has been insufficient to compare the predictive value of different NHs. Val-HeFT evaluated the efficacy of valsartan in 5010 patients with NYHA class II to IV HF, and measured several NHs at baseline, providing an opportunity to examine this relationship.
Methods: Plasma aldosterone (Aldo), brain natriuretic peptide (BNP), norepinephrine (NE) and renin activity (PRA) were measured prior to randomization. The risk ratio (RR) for mortality and non-fatal morbid events(i.e. cardiac arrest resuscitated, hospitalization for HF, IV inotropes or vasodilators for at least 4 hours) was calculated for patients with baseline values >= vs < the median, using a Cox proportional hazard model with baseline NH category as a covariate. Data was analyzed for all patients independent of study group.
Results: Plasma concentrations of individual NHs were available for 4305 patients, with mean (±SD) age 63±11y, 38% in NYHA class III-IV, and mean ejection fraction 27±7%. The risk ratios (RR) for individual NHs (>=median vs. <median) are reported in the table. Patients with baseline NH concentrations above the median had significantly higher risk of dying or having a non-fatal morbid event over a mean follow-up of 23.0 months, when compared to patients with NH below the median. BNP had the highest values for RR and patients with baseline BNP >=97 pg/mL had a greater than 2-fold increase in mortality and non-fatal morbid event.

		RR (95% confidence intervals)	
NH	baseline median	mortality	non-fatal morbid events
Aldo	101 pg/mL	1.13 (0.98-1.30)	1.40 (1.21-1.63)
BNP	97 pg/mL	2.47 (2.12-2.87)	2.97 (2.53-3.49)
NE	394 pg/mL	1.74 (1.51-2.01)	1.59 (1.37-1.84)
PRA	5.3 ng/mL/h	1.44 (1.25-1.65)	1.27 (1.09-1.46)

Conclusions: Whereas all 4 NH are significant prognostic markers in HF, plasma BNP provides the greatest distinction between high and low risk for morbidity and mortality.

1479 Prolonged survival and fewer readmissions: the long-term effects of a home-based intervention in chronic heart failure

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Background: Although post-discharge programs of care for patients with chronic congestive heart failure (CHF) prolong event-free survival, reduce readmissions and lower costs in the short-term, it is not known to what extent initially observed benefits persist in the longer-term, nor whether such programs positively influence survival.
Methods: We prospectively studied the longer-term effects of a multidisciplinary home-based intervention (HBI) in a composite cohort of typically older CHF patients randomly allocated to either HBI (n = 149) or usual care (n = 148) as part of two closely related randomized studies. As before, we used a primary end-point of time to unplanned readmission or death (event-free survival) on an "intention-to-treat" basis. Other study endpoints included the total number of unplanned readmissions and associated stay, health care costs and all-cause mortality.
Results: During a median of 4.2 years of follow-up, the primary endpoint occurred in 130 (87%) HBI vs 135 (91%) usual care patients. Median event-free survival was more prolonged in the HBI group compared to usual care (7 versus 3 months: $P < 0.01$). Fewer HBI patients died during follow-up (56% vs 65%: $P = 0.06$) and had more prolonged survival (median survival 40 vs 22 months: $P < 0.05$) compared to usual care. Assignment to HBI was both an independent predictor of event-free survival (RR 0.70: $P < 0.01$) and survival alone (RR 0.72: $P < 0.05$). Overall, HBI patients had 78 fewer unplanned readmissions compared to usual care patients (397 vs 475 - a mean of 0.17 vs 0.29 readmissions/month: $P < 0.05$). HBI patients also had a shorter average length of stay and were admitted to less expensives units. Despite more prolonged survival, therefore, HBI patients had 1003 fewer days of readmission (3,123 vs 4,126 - a mean of 1.2 vs 2.3 days/patient/month: $P < 0.001$) and the median total cost of these readmissions per HBI and usual care patient, respectively, was $A325 vs $A660/month ($P < 0.01$).
As such, the cost of initially providing greater levels of health care to HBI patients (about $A600/patient) proved to be less than 10% of total cost-savings in the longer-term ($A7000/HBI patient).
Conclusions: This is the first study to show that the beneficial effects of HBI in reducing frequency of unplanned readmissions in CHF persist in the longer term and are associated with prolongation of survival. These data provide further compelling evidence for the application of this type program as part of the gold-standard post-discharge management of CHF.

1480 Prevalence and prognostic role of anemia in patients with heart failure in the IN-CHF Registry and the Val-HeFT trial

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Background: In the Framingham Study, anemia was an independent risk factor for the development of heart failure (HF), and in SOLVD it was an important predictor of mortality. Moreover, correction of mild to moderate anemia has recently been shown to improve HF. In the present study we assessed the prevalence and prognostic role of anemia in two separate populations: (a) relatively unselected patients in clinical practice (IN-CHF), and (b) a more selected population randomized to Val-HeFT.
Methods: There were 2411 ambulatory patients with HF that were monitored prospectively in a community setting (IN-CHF), and 5010 patients randomized in Val-HeFT. Anemia was defined as a hemoglobin (Hb) level < 11 g/dl in women, < 12 g/dl in men. Univariate and multivariate analyses were performed separately in Val-HeFT and IN-CHF databases to evaluate the prognostic role of anemia.
Results: In the IN-CHF registry there were 15.5% of patients with anemia as compared with 9.9% in Val-HeFT. In both databases patients with anemia were older, had more severe functional impairment, higher ischemic etiology of HF, greater serum creatinine and lower body mass index than patients without anemia. In the IN CHF registry the one-year all-cause mortality was significantly higher in anemic (25.8%) as compared to non-anemic (13.2%) patients ($p<0.0001$), and anemia was an independent risk factor for 1 year mortality in a multivariate analysis (RR 1.59, 95%CI 1.19-2.13).
In Val-HeFT the all cause mortality during the follow-up period of 23.0 months was significantly higher in anemic patients (29.6%) as compared to patients without anemia (18.5%, $p<0.0001$). Even after adjustment for other factors, anemia remained an independent predictor of mortality (26% higher than that of non anemic subjects, RR 1.26, 95%CI 1.04-1.52).
Conclusions: These data confirm that anemia is common in HF patients in the community. Lower incidence of anemia in clinical trials of HF is probably because of exclusion criteria. In both populations, anemia remains an independent predictor of mortality.

1481 Prevalence, characteristics and prognostic signficance of anaemia in heart failure

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Background: There are few data examining the clinical and prognostic significance of anaemia in patients with chronic heart failure (CHF).
Methods: Using the unique Scottish Morbidity Record linkage scheme, we examined the prevalence, characteristics and prognostic significance of anaemia in all patients with a first-ever admission for CHF (principal diagnosis) in Scotland during 1990-1995. We also specifically examined the relationship between renal dysfunction and anaemia in a cohort of 291 CHF patients from Australia and Scotland.
Results: During the period 1990-95 a total of 20,049 men and 22,664 women were discharged for the first-time with a principal diagnosis of CHF in Scotland. A secondary diagnosis of anaemia was recorded in 2.8% (0.9% iron deficient) of male and 4.5% (1.3% iron deficient) of female discharges. Non-specific anaemia was the most common form of anaemia recorded. The strongest independent correlate of non-specific anaemia was a concurrent diagnosis of renal disease – the adjusted OR (95% CI) being 2.9 (2.1, 3.9: $P < 0.001$) in men and 3.2 (2.5, 4.2: $P < 0.001$) in women. In the short term, a concurrent coding of both iron deficient anaemia and non-specific anaemia was associated with a significantly better prognosis ($P < 0.001$ for all comparisons). The adjusted risk of death within 30-days of admission associated with iron deficient anaemia was 0.31 (0.18-0.53) in men and 0.39 (0.26-0.59) in women. The equivalent adjusted risk for non-specific anaemia being 0.59 (0.44-0.79) and 0.65 (0.52-0.79). Conversely, whilst the risk of death within 30 days to 2 years was equivalent for those patients with iron deficient anaemia, compared to the rest, non-specific anaemia was associated with an adjusted increased risk of death in both men (OR 1.36; $P < 0.01$) and women (OR 1.21; $P < 0.05$). In the cohort of 291 CHF patients subject to greater scrutiny, we identified a significant, inverse correlation between serum creatinine and haemoglobin levels:in men the R squared was 0.05 ($P < 0.001$) for these two parameters and in women 0.23 ($P < 0.001$) with higher creatinine levels being associated with lower haemoglobin levels in this cohort.
Conclusions: Anaemia is prevalent in CHF patients presenting to hospital for the first time. Non-specific anaemia is commonly associated with renal disease with a strong correlation between higher creatinine and lower haemoglobin levels. Whilst iron-deficient anaemia is associated with better survival rates, non-specific anaemia is independently associated with higher mortality rates in the medium-term.

ASSESSMENT OF LEFT VENTRICULAR FUNCTION BY TISSUE DOPPLER

1505 Local myocardial contraction characteristics in mitral valve prolapse detected by colour tissue Doppler, strain rate and strain imaging

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In patients with mitral valve prolapse (MVP) whether a local heterogeneity in the systolic contraction related to papillary muscle (PM) tracking is controversial. We aimed to assess local longitudinal contraction of LV and PM in MVP using the individual curves of tissue Doppler velocity (TV) and velocity time integral (TVTI), strain rate (SR), strain (epsilon), the time from R-wave to the occurrence of compression/expansion cross-over (TCEC),and tissue density(TD). Study population comprised 25 patients with classical MVP(mean age 40±12).Curved M-mode data were obtained from apical views, and TCEC was measured.Individual longitudinal curves of TV,TVTI, SR, epsilon and TD data were extracted. Peak TV and TVTI were significantly higher for basal lateral and septal LV segments compared with other segments and PM ($p<0.01$). Moreover, both TV and TVTI curves revealed a significant midsystolic peak in the mid lateral and medial LV segments, and a late systolic peak within the PM ($p<0.05$). Late systolic TV peak (up to 10 times compared with baseline, $p<0.001$) within the PM was found to be increased from PM base to chordal insertion points ($p<0.05$). Distinctive mid and late systolic peaks related to mid LV segments and PM were also evident in the SR and epsilon curves. Curves extracted from mid and basal LV,and PM showed that SR was the highest at late systole ($p<0.001$) and increased up to 8-10 times compared with baseline ($p<0.001$).Epsilon curves revealed a distinct and late systolic peak lower than initial peak values ($p<0.05$). Individual TD density curves also disclosed a second late systolic decrease related to PM,mid and basal LV segments ($p<0.05$). However, longitudinal TCEC curves from LV segments, and PM showed no local difference ($p>0.05$).

In conclusion, individual TV,TVTI, SR, epsilon,and TD curves suggest that systolic contraction may offer spatial and temporal difference within the LV wall and PM in patients with MVP. Results seem to be consistent with mid and late systolic increase in local deformation related to papillary muscle tracking by prolapsed mitral leaflets.

1506 Regional myocardial work index by strain Doppler echocardiography and left ventricular pressure – a new method for quantifying myocardial function

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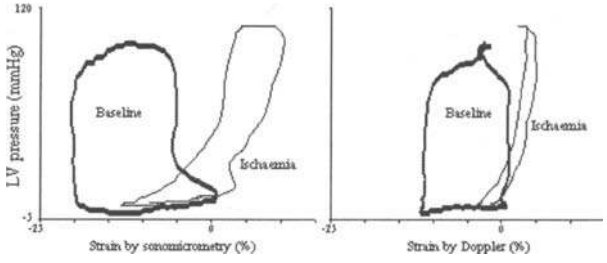
Background: There is need for better methods to quantify regional myocardial function. In the present study we investigate the feasibility of quantifying regional function in terms of a segmental myocardial work index as derived from strain Doppler echocardiography (SDE) and invasive pressure.

Methods: In 6 anaesthetized dogs we measured LV pressure by micromanometer and myocardial longitudinal strains by SDE and by sonomicrometry. The regional work index was calculated as the area of the pressure-strain loop. Measurements were done during baseline, during intravenous volume loading and during myocardial ischaemia. The figure shows representative pressure-strain loops by the two methods. The area of the LV pressure-strain loop using sonomicrometry was used as reference method.

Results: LV end-diastolic pressures at baseline, during volume loading and LAD occlusion were 6.3 ± 1.1 (± SEM), 20.0 ± 2.1 ($P<0.01$) and 6.4 ± 1.4 mmHg (NS), respectively. Volume loading increased the pressure-strain area from 1.3 ± 0.2 to 2.4 ± 0.2 kJ/m^3 using SDE and from 1.5 ± 0.3 to 2.7 ± 0.3 kJ/m^3 using sonomicrometry, and ischaemia caused a decrease to 0.4 ± 0.1 and 0.6 ± 0.2 kJ/m^3, respectively. The regional work index by SDE correlated well with sonomicrometry ($y=0.70x + 158$, $r=0.80$, $P<0.01$).



Conclusions: A regional myocardial work index can be estimated by SDE in combination with LV pressure. This approach should be tested clinically, and could represent a new method for on-line assessment of myocardial tissue viability during invasive studies.

1507 Myocardial acceleration during isovolumic contraction – Is it really a sensitive index of myocardial function?

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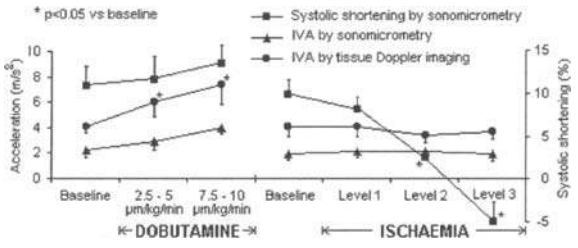
Introduction: Myocardial acceleration during isovolumic contraction (IVA), as measured by tissue Doppler imaging (TDI), has been introduced as an index of myocardial contractility. The present study investigates the ability of IVA to reflect changes in regional myocardial function during global enhancement of contractility and during regional myocardial dysfunction.

Methods: In 6 anaesthetized dogs we measured pressures, myocardial long axis velocities by TDI (133-184 Hz), and segment lengths by sonomicrometry (200 Hz). Peak IVA was calculated from the TDI data and the sonomicrometric dimension data (from the positive IVC velocity spike). Measurements were done during baseline, IV dobutamine, and at 3 levels of regional myocardial ischemia (reductions in LAD flow).

Results: Dobutamine infusions increased LV dP/dt max by 121 ± 33% (± SEM, $p<0.05$) and Doppler IVA by 3.3 ± 1.2 m/s2 ($p<0.05$). At ischaemia level 2 there was a marked reduction in systolic shortening by 80 ± 15% ($p<0.05$). At ischaemia level 3 the segments became dyskinetic. (Figure). Doppler IVA, and LV dP/dt max were unchanged at all levels of ischemia. Doppler IVA correlated with IVA by sonomicrometry ($r = 0.67$, $p<0.01$). IVA by sonomicrometry occurred 26 ± 2 ms after start of IVC and at a LV pressure of 13.9 ± 0.8 mmHg.



Relation of QRS- and IVD-Shortening

Conclusions: Consistent with previous reports, myocardial acceleration during isovolumic contraction reflected global changes in LV inotropy. However, IVA did not reflect regional myocardial dysfunction during ischaemia. IVA occurred near end-diastole, and one should consider if IVA may reflect LV end-diastolic wall oscillations rather than intrinsic myocardial contractility.

1508 Patients with a hypertensive response to exercise have impaired systolic and diastolic function

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Background: A hypertensive (HT) response to exercise predicts the development of chronic hypertension and may represent an early sub-clinical stage of the disorder. We sought whether subtle abnormalities of myocardial function could be detected in these pts with sensitive new echo techniques.
Methods: The study included 52 subjects: 37 pts (age 55±10yrs) with a HT exercise response (BP >210/105mmHg in males; >190/105mmHg in females), normal LV ejection fraction and a negative stress ECG or stress echo and 15 age-matched controls with a normotensive exercise response. Assessment of diastolic function utilized transmitral and pulmonary vein Doppler, flow propagation velocity (color M-mode) and mitral annular velocities. Mean values for cyclic variation (CV) of integrated backscatter (IB), strain rate (SR) and peak systolic strain were averaged from individual segments using Color tissue Doppler imaging (Vingmed System Five) in 3 standard apical views.
Results: Pts with a HT exercise response had mildly reduced exercise performance compared with controls (Bruce protocol duration 8.5±2.7 vs. 10.2±2.2 min, p=0.04). LV mass index was similar, but resting BP was higher and some, but not all, parameters of diastolic function were impaired in HT exercise response pts (table). Peak systolic strain, SR, and CV, were significantly lower in pts compared with controls indicating systolic dysfunction (table).

	Controls	HT Exercise Response	p
Mean resting BP (mmHg)	86±6	104±16	0.0002
LV Mass Index (g/m^2)	81.0±14.4	88.9±19.0	0.16
E wave Deceleration Time (msec)	201±24	223±34	0.028
Flow Propagation Velocity (cm/s)	79±17	64±22	0.024
CV (dB)	7.63±1.04	6.37±0.96	0.0001
SR (1/s)	-1.97±0.25	-1.47±0.22	<0.00001
Peak Systolic Strain (%)	-30.6±3.6	-25.7±3.4	0.00002

This difference in reduction of IB and strain parameters was equally apparent in pts with and without a history of resting HT.
Conclusions: A HT response to exercise is associated with abnormalities of myocardial function, even in the absence of a clinical history of hypertension. Such abnormalities may represent early changes of hypertensive heart disease.

1509 "Pure" diastolic dysfunction: does it ever exist?

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"Pure" diastolic dysfunction is usually diagnosed when Doppler assessment of transmitral flow is abnormal but the left ventricular (LV) ejection fraction (EF) is normal. Transmitral flow reflects global filling, and it becomes abnormal once >50% of LV segments have impaired relaxation. EF may be measured accurately by planimetry, or it may be inferred from fractional shortening which measures only radial function. Longitudinal function, governed by subendocardial fibres, is more sensitive as a marker of early changes in systolic function with age or disease.
Aim: To investigate the correlation between global diastolic dysfunction and regional (radial and longitudinal) systolic function.
Methods: Fifty subjects (15 with hypertrophic cardiomyopathy, 15 with hypertension, and 20 normal subjects, of similar age, 38±10, 44±7, 39±12 years, and EF, 65±8, 64±7, 66±6%) were studied by conventional and tissue Doppler echocardiography. Global diastolic dysfunction was assessed from the flow propagation velocity into the LV by colour M-mode (FPV), from the mean early diastolic velocity of the mitral annulus (Etde), and from its ratio with the transmitral E wave velocity (E/Etde); and global systolic function by measurement of EF (Simpson's rule). Radial and longitudinal function were assessed separately from the posterior wall (PLAX view) and from mitral annular velocities (mean of 4 sites - Stde, apical views).
Results: Global diastolic function correlates (r) with longitudinal systolic function (*p<0.01), but not with radial or global systolic function (table). From 25 patients with isolated diastolic dysfunction (FPV<45 cm/s or Etde<8 cm/s), 23 (92%) also had longitudinal systolic dysfunction (Stde<9 cm/s).

Systolic vs. diastolic LV function

Systolic function	FPV	Etde	E/Etde
Longitudinal	0.41*	0.65*	0.60*
Radial	0.09	0.04	-0.11
Global (EF)	0.04	0.12	0.05

Conclusion: Global "diastolic dysfunction" is strongly associated with a progressive decline in longitudinal systolic function. This suggests that "pure" diastolic dysfunction is diagnosed erroneously when systolic function is assessed by old echocardiographic techniques. Tissue Doppler longitudinal velocities reveal more subtle changes of systolic function.

1510 Early diastolic mitral annulus velocity is superior to flow propagation velocity in assessment of left ventricular diastolic function

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Background: Pulsed wave tissue Doppler echocardiography (PW-TDE) and color M-mode are novel Doppler methods used for left ventricular (LV) diastolic function assessment. Until now only few studies compared accuracy of these methods in the same series of patients.
Objectives: To determine the utility of PW-TDE and color M-mode parameters in distinguishing abnormal LV diastolic function in patients with various cardiovascular diseases and to compare their discriminating power.
Methods: Early diastolic mitral annulus velocity (Em) determined by PW-TDE and color M-mode flow propagation velocity (Vp) were measured in 86 male patients with clearly defined LV filling pattern type by using standard Doppler indices. Values of Em < 0,08 m.s-1 and Vp < 0,5 m.s-1 were considered to detect abnormal LV diastolic function. Receiver operating characteristics (ROC) curves of Em < 0,08 m.s-1 and Vp < 0,5 m.s-1 were compared by assessing the areas under the curve (AUC), the sensitivity and the specificity were calculated by using standard formula.
Results: A value of Em < 0,08 m.s-1 distinguished abnormal LV diastolic function with higher sensitivity and specificity than Vp < 0,5 m.s-1 (96% and 87% vs. 73% and 84%, respectively). Comparison of ROC curves showed significant difference between AUC on behalf of Em (p < 0,01). In stepwise multiple logistic regression analysis, pseudonormal filling pattern and EF > 60% were identified as significant predictors of Vp false negative results (p < 0,05).
Conclusions: Em appears to be superior to Vp in detection of LV diastolic dysfunction. Vp fails to detect abnormal LV filling in particular in patients with preserved LV systolic function and pseudonormal filling pattern type.

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1512 Long-term biventricular pacing reduces pulmonary capillary filtration pressures. A study using carbon-11 acetate positron emission tomography

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Background: Biventricular pacing (BiV) improves symptoms in patients with severe heart failure and intraventricular conduction delay and has been shown to acutely reduce ventricular filling pressures. Whether long term BiV reduces the extent of pulmonary congestion is unknown. To investigate this, we studied the first pass net lung retention rate of 11C-acetate as an index of the pulmonary capillary filtration pressure.
Methods: Six patients (56±10y, EF 22±9%) with severe CHF due to ischemic heart disease (n=3) or dilated cardiomyopathy (n=3), successfully treated with BiV for at least six months, were assessed by 11C-Acetate-PET first at baseline (BiV "on") and after a 2 weeks treatment cessation (BiV "off"). Patients were also evaluated by two-dimensional echocardiography, Brain Natriuretic Peptide (BNP), the six minute walk test and a quality of life questionnaire (Minnesota).
Results: The rate of fist pass acetate-retention in lung tissue was significantly increased when BiV was "off" as compared to "on" (0.039 ± 0.015 and 0.023 ± 0.013 ml/min/ml respectively; p<0.05), indicating an increased pulmonary congestion. In parallel, BNP (+69%, p<0.05) and the left ventricular enddiastolic diameter (+3 mm, p< 0.05) increased between "on" and "off". There was a trend towards a decreased walking distance and QoL.

	11-acetate lung retention (ml/min/ml)	BNP (ng/l)	LVEDD (mm)	6'walk (m)	QoL (score)
BiV "on"	0.023±0.013	110±100	69.0±13.3	517±349	16±8
BiV "off"	0.039±0.015	186±143	71.8±12.9	487±333	22±8
p-value	p<0.05	< 0.05	< 0.05	ns	. ns

Conclusions: This study shows for the first time, that pulmonary capillary filtration pressures and, thus, the extent of pulmonary congestion can be reduced by long term biventricular pacing. This finding is in agreement with recent reports on increased exercise capacity, quality of life and functional class by BiV.

1513 QRS-complex shortening as predictor for electromechanical restoration in heart failure patients with cardiac resynchronization therapy (Cardiac Resynchronization Therapy)

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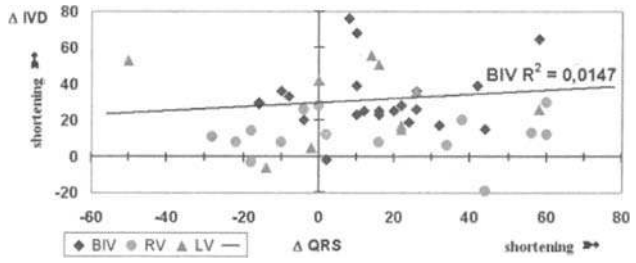
So far there is diverging information about the value of QRS shortening to optimize left ventricular (LV) pacing site and AV delay in patients with congestive heart failure and left bundle branch block undergoing electrical resynchronization therapy.The aim of the investigation was to evaluate the correlation between QRS change and the change in the interventricular electromechanical delay (IVD) measured by Doppler echocardiography.

Methods: 25 patients (QRS 180ms; EF 27%) were implanted with a CRT device suitable for either LV or biventricular pacing (BIV). Optimal AV delay was determined invasively by the maximum increase of pulse pressure during the implant procedure and/or confirmed by Doppler echocardiography according to Ritter's method.The IVD's were assessed by the onset of pulmonary and aortal flow either under sinus rhythm with intrinsic conduction or under different pacing conditions (RV; LV; BIV). 12-lead-ECG was reported parallel and QRS width averaged in II, V1 and V6 three times.

Results: The IVD under sinus rhythm with intrinsic conduction was 65±18.6ms. It was significantly reduced by LV pacing (-65%; $p<0.001$) and BIV pacing (-45%; $p<0.001$), whereas RV stimulation does not change the IVD (-8%;p=0.24). In contrast BIV stimulation showed the largest reduction in QRS width (-8%;p=0.02). Neither LV (-3%; p=0.22) nor RV-pacing (-1,3%; p=0.41)caused a significant change of QRS width. Only in a minority (n=3) was QRS width reduced below 140 ms.



Relation of QRS- and IVD-Shortening

Conclusion: The largest reduction of IVD was achieved by LV pacing, whereas the greatest reduction in QRS width was observed under BIV. No correlation exists between QRS shortening and electromechanical restoration.
Therefore QRS shortening seems not to be a helpful tool to optimize cardiac resynchronization.

1514 PATH-CHF II: Cardiac Resynchronization Therapy using haemodynamically optimized univentricular pacing in heart failure patients stratified by severity of ventricular conduction delay

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The PATH-CHF II multi-center trial assessed clinical efficacy of cardiac resynchronization therapy (CRT) using hemodynamically optimized univentricular pacing in patients (pts) with mild to severe heart failure, with or without ICD indication, who were prospectively stratified by severity of ventricular conduction delay.

Method: The design was a randomized controlled crossover (3 months CRT on and 3 months off) with equal distribution of pts having QRS duration > 150 ms (Group I) or between 120 and 150 ms (Group II). 89 pts were implanted with hemodynamically optimized univentricular VDD pacing (LV pacing: 86, RV pacing: 3). Mean age: 60 ± 9 years, 59 males, mean LVEF 22 ± 8%, mean QRS interval 156 ± 21 ms, NYHA class II/III/IV: 29/59/1. Primary endpoints were peak oxygen uptake (VO2p), oxygen uptake at anaerobic threshold (VO2at) and 6-minute walk distance. Secondary endpoints included quality of life (QOL) score assessed by the Minnesota Living with Heart Failure questionnaire.

Results: The effect of CRT was significant for all endpoints for the whole population, as well as for Group I ($p<0.05$). Significance was not reached in Group II for any endpoint.

Conclusions: The PATH-CHF II trial demonstrates significant clinical improvement in mild to severe heart failure pts. Benefit associated with 3 months of CRT depends on magnitude of baseline QRS interval. However, longer term data are required to confirm these findings. Further analyses are also needed to identify other parameters predictive of CRT benefit, especially in narrow QRS patients.

Results of Groups I and II

Endpoints	Sequence	Group I CRT	Group I No treatment	Group II CRT	Group II No treatment
VO2p (ml/kg/min)	A	15.6 ± 3.6	13.0 ± 3.5	14.5 ± 2.5	14.1 ± 2.4
	B	15.6 ± 2.8	13.6 ± 3.1	15.3 ± 3.4	15.0 ± 3.4
VO2at (ml/kg/min)	A	10.5 ± 2.5	8.9 ± 2.0	10.4 ± 2.0	9.9 ± 2.0
	B	10.8 ± 1.4	9.4 ± 1.4	10.0 ± 2.5	10.0 ± 2.4
6 min walk (m)	A	462 ± 79	407 ± 117	413 ± 81	411 ± 60
	B	448 ± 69	411 ± 61	488 ± 93	479 ± 68
QOL (score)	A	24 ± 19	32 ± 27	22 ± 18	23 ± 23
	B	17 ± 13	24 ± 15	23 ± 21	24 ± 14

Sequence A: pts with active CRT during the first 3 month period. Sequence B: pts with active CRT during the second 3 month period.

COMPUTER DEMONSTRATION

1525 Comparison of different video compression algorithms for angiographic data: a web based approach

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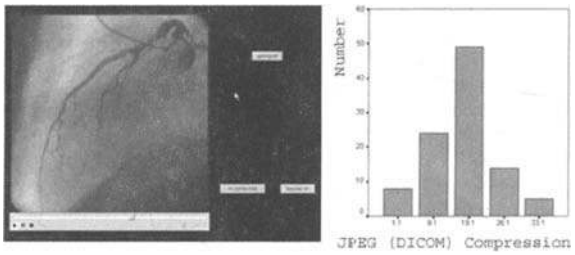
Background: A compression of angiographic data is obligatory for Internet based applications, e. g. telemedicine, due to the limited network bandwidth. We developed a web based user interface to rate the image quality of different compression algorithms.

Methods: The angiographic data set used for comparison consists of 10 coronary angiograms each of them compressed with 8 different algorithms and 6 different compression ratios. In addition, each set contains the uncompressed data as a reference. Compression algorithms used are JPEG (Joint Photographic Experts Group), JPEG 2000, 2 different MPEG (Motion Picture Experts Group) implementations and 3 proprietary video streaming formats.
We designed a web based user interface to simultaneously display and rate the individual angiographic cases (see table). The rater selects the minimum quality required for diagnostic purposes by switching backwards and forwards through the quality steps (resulting from the different compression ratios). The results are stored in a database which allows for a graphical presentation and additional statistical analyses.

Results: 10 physicians rated 490 films
– none of them had problems using the interface
– the rating took 43 min. on average (from 25 to 75 min.)
– rapid display of statistics, e.g. number of adequate JPEG films (see table, 8x 1:1, 24x 9:1, 48x 19:1, 14x 26:1, 4x 33:1)
– high volume raters (>2500 coronary angiographies) selected significantly more high compressed images as adequate 55,8% vs 35,7%.



User interface and database result.

Conclusion: Our web based approach enables experts to compare different compression algorithms, independently from where they reside. Therefore, it is predestined for multicenter studies on medical image compression over the Internet.

1526 Quantitative three-dimensional intravascular ultrasound: improvements towards (semi-) automated border detection including the stent border

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Background: IntraVascular UltraSound (IVUS) is a catheter-based technique, which provides real-time high-resolution images of the arterial wall. The technique is used very often for clinical research studies to measure in-stent restenosis. The technique is used often to monitor the stent placement or to visualize in-stent restenosis. Automation of the boundary detection of the stent, lumen, and vessel reduces the required analysis time and the subjectivity of the manual tracing procedure. The three-dimensional reconstruction permits an advanced assessment of the morphology.
Methods: The user is able to define the distal, proximal and main segment in which the boundaries are detected. If a stent is present, the procedure starts with the automated detection of the stent boundary. The detection method is able to correct itself based on the expected location of the stent struts and uses a three-dimensional model and the approximately circular appearance of the stent. By on-line presenting the area data graphically, the user immediately gets feedback about the quantitative results. Next the vessel and lumen detection is performed, based on a combination of transversal and longitudinal contour detection techniques using a model of the vessel and knowledge about the morphologic structures. The possible errors easily can be corrected by minimal user-interaction.
Results: In a set of 200 slices from different pullback series (acquired with Boston Scientific and EndoSonics equipment) the automatically detected stent boundaries were compared to manually drawn stent boundaries. The comparison of the cross-sectional stent areas for the manually traced and automatically detected boundaries resulted in an r-value of 0.99. In a set of 50 pullback runs (acquired with Endosonics equipment) the entire stented segment was analyzed automatically and the most distal and the most proximal slice in a continuous series of slices containing stent struts was selected to assess the stent length. The comparison of these distances with the original stent lengths resulted in an average overestimation of 0.35 ± 1.42 mm by IVUS. The start and end point of a stent are not well defined because the catheter moves in and out the stent, due to cardiac motion.
Conclusion: Due to the flexible use of more than two longitudinal cutplanes and the advanced knowledge-guided contour detection approach, the new IVUS analysis system has proven to be suitable for clinical research studies. The inclusion of the stent boundary will be very useful for in-stent restenosis studies, e.g. the effect of drug-coated stents.

POSTER DISPLAY III

MODERATED POSTER SESSION III

P1527 Noncompaction of the ventricular myocardium in a paediatric population: study up-date and developmental considerations

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Background: Noncompaction of the ventricular myocardium (NCVM) is a rare developmental disorder defined by morphological criteria. The reported morbidity and mortality is considerable.
Purpose: To evaluate the prevalence, associated cardiac features, and implications of NCVM in a pediatric population.
Methods: All patients consecutively examined by echocardiography at our institution between 9/1999 through 12/2001 were evaluated.
Results: 64 of 4.913 patients (1.3%) aged 3days-21years were diagnosed. The gender ratio was 0.83 (f:m). There was consistent affection of the left ventricular apex (100%). Besides NCVM, 21 patients (33%) had a normal cardiac anatomy while 43 patients (67%) suffered from congenital heart defects (CHD). Patients with isolated NCVM were younger than CHD patients. In the first group, 12 patients (57%) had a dilated hypocontractile left ventricle. 2 patients died (4.7%). In the CHD group, 4 patients (9.3%) had a compromised left ventricular function with dilatation. Morphologically, 37 patients (86%) had some kind of left sided, 12 patients (30%) some kind of right sided obstruction. In all 8 patients with VSDs there was affection of the muscular septum (100%). No atrioventricular septal defect, transposition of the great arteries, or truncus arteriosus communis was seen along with NCVM. Neither was NCVM seen in dilated cardiomyopathy following myocarditis. Arrhythmia was found in 3 patients (4.7%), thrombi and embolization in one each (3.1%).
Conclusion: NCVM appears to be more frequent than suspected. Congestive heart failure is common, particularly along with isolated NCVM, while other complications are rare. The coincidence of selected CHD associated with NCVM is striking. Potential developmental implications are discussed. Fetal, histo-pathological, and follow-up studies are sought.

P1528 Targeted disruption of the annexin 6 gene improves resistance to hypoxia injury in the adult mice cardiaomyocyte

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Annexin 6 is one of a family of Ca^{2+}-dependent phospholipid-binding proteins. The function of annexin 6 is poorly understood, although it has been known that annexin 6 acts as a regulator of intracellular Ca^{2+} and other ion channels, and potentially as an ion channel of the cell. Annexin 6 has been shown in vitro to have a modulatory effect on the SR calcium-release channel, cardiac L-type calcium channel and Na^{+}/Ca^{2+} exchanger. To investigate the possible cardio-toxic and/or cardio-protective effects of annexin 6 in hypoxic conditions, we examined lactate dehydrogenase (LDH) levels in myocytes isolated from mice with targeted disruption of the annexin 6 gene (knockout, KO, n=6, age=12 weeks) and wild type mice (WT, n=6, same age), as well as myocyte live percentage. After isolation then eight hours hypoxia, LDH released by myocytes from annexin 6 KO mice was significantly lower than that from WT animals (0.442±0.031 vs 0.531±0.057, LDH injury index, KO vs WT, mean±SD, $P<0.01$). Eight hours of reoxygenation after eight hours hypoxia further increased LDH levels in both experimental groups, but the significant difference between KO and WT mice remained (0.547±0.073 vs 0.633±0.024, $P<0.05$). In the end of reoxygenation, percentage of live cells was markedly higher in annexin 6 KO group compared to that in WT group (based on a 400-cell count, 44.75±2.99% vs 28.50±2.87%, $P<0.01$). These data indicate that the absence of annexin 6 in the mice may improve myocyte viability and increases cell resistance to hypoxic stress.
It has been reported that human end-stage heart failure is associated with depressed annexin 6 in mRNA and protein levels. We have demonstrated that mechanical properties and Ca^{2+} extrusion and uptake are increased in myocytes from the annexin 6 gene knockout mice. Taken together, these findings suggest that the annexin 6 may play an important role as a negative regulator, not only in intracellular Ca^{2+} cycling and myocyte mechanics, but also in protection of cardiomyocyte. The inhibition of annexin 6 may benefit cardiac functions.

P1529 In vitro culture of muscle derived stem cells for application in human cardiac regenerative therapy by means of cellular cardiomyoplasty

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Animal studies as well as some preliminary clinical data suggest that transplantation of autologous myoblast (cellular cardiomyoplasty) may result in improvement of cardiac function after myocardial infarction. The purpose of our study was to optimize and upgrade the in vitro culture of autologous myoblast for clinical application. Muscle biopsies from 15 patients undergoing cardiac surgery were obtained. Satellite cells were isolated by enzymatic digestion, culture in Ham F12 media supplemented with human serum and without growth factors. Cells underwent a preplating step on day +6 to deplete fibroblast from the culture. Muscle progenitor cells (myoblast) were identified by their expression of NCAM (CD56), lack of expression of CD45 and the presence of desmin in the cytoplasm by flow cytometry and immunohistochemistry. After preplating, the percentage of CD56+/CD45- cells was 44.12% ± 1.44 (mean ± SEM) while the percentage of desmin positive cells was (40% ± 1.1) (mean ± SEM, correlation > 90%). Samples in which myoblast purity was below 30% were subjected to a positive CD56 cell selection using magnetic immunobeads (MILTENYI). After selection myoblast purity was always greater than 90%. Culture was continued after cell selection. We assessed the effect of serum or plasma concentration, degree of confluence and the number of days in culture. We compare the yield between samples with (group 1) and without (group 2) selection. Cell yield (number of CD56 cells/gram of muscle) was not significantly different between group 1 and 2 (53.1 x 106 ± 2.7 and 49.5 x 106 ± 4.3, respectively), but there were significant differences in percentage of CD56 cells (85.9 ± 2.1 and 36.3 ± 7.6; $p < 0.05$). However, serum concentration below 10% resulted in a significantly reduce cell yield. In conclusion, we demonstrate that enough muscle progenitor cells can be obtained from a 5 grams muscle biopsy for cellular cardiomyoplasty provided there is more than 10% of human serum. Cell selection based on expression of CD56 antigen is a potential way to increase myoblast purity and deplete unwanted fibroblast. The culture system has been scale up for clinical purposes.

P1530 Comparative effects of candesartan and enalapril on left ventricular hypertrophy in patients with essential hypertension: the CATCH study

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Background: A limited number of studies evaluated the effect of angiotensin II receptor antagonists (AIIAs) on left ventricular hypertrophy (LVH) in comparison with other antihypertensive drugs,and no large study has compared AIIAs with angiotensin converting enzyme inhibitors (ACEIs).
Methods and Results: The CATCH (Candesartan Assessment in the Treatment of Cardiac Hypertrophy) study was a multicenter prospective randomized double-blind trial comparing the effects of candesartan cilexetil (8-16 mg o.d.) and enalapril (10-20 mg o.d.) with possible addition of hydrochlorothiazide (12.5-25 mg o.d.) on echocardiographic left ventricular mass index (LVMI), in 239 hypertensives with LVH (LV mass index, LVMI > 120 g/m^2 in men and >100 g/m^2 in women). Two dimensionally guided M-mode echocardiograms were carried out at screening (recruiting scan) randomization (baseline scan) and after 24 and 48 weeks of treatment.Baseline and treatment echocardiograms were read at two central labs without knowledge of the scan time sequence.In intention to treat (ITT) analyses (196 patients), systolic and diastolic blood pressures (SBP,DBP) were significantly and equally reduced by two treatments. Candesartan and enalapril reduced LVMI to the same extent,i.e. by 15.0, and 13.1 g/m^2 (-10.9 and -8.4%), ($p<0.001$ for both). The proportion of patients achieving normalization of LVMI was non-significantly higher with candesartan (36.3 vs 28.6%). Similar results were obtained in per protocol (PP) analyses.Cough incidence was lower with candesartan ($p<0.03$).
Conclusions: CATCH is the first large study comparing the effects of an AIIA and an ACEI on LVMI. Candesartan cilexetil was found equally effective as enalapril in reducing SBP,DBP and LVMI in hypertensives with LVH, according to both ITT and PP analyses.

P1531 Peroxisome proliferator-activated receptor gamma activators inhibit mechanically-induced hypertrophy in cardiac myocytes

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Background: Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily. PPAR gamma, one of three members of PPARs, inhibits growth and migration in vascular smooth muscle cells. The natural prostaglandin D2 metabolite, 15-deoxy-delta12,14-prostaglandin J2 (15d-PGJ2) and synthetic antidiabetic thiazolidinedione (troglitazone) are ligands for PPAR gamma. PPAR gamma mRNA is present in cardiac myocytes; however, whether PPAR gamma affects cardiac hypertrophy remains unknown.
Methods and Results: We investigated the effects of PPAR gamma activators on cardiac hypertrophy in cultured neonatal rat cardiac myocytes. Cyclic 4% biaxial mechanical strain caused enlargement of the cardiac myocytes (1.3 ± 0.1 fold versus control, $P<0.0001$), but the PPAR gamma activators troglitazone and 15d-PGJ2 (10 μM) inhibited this effect (troglitazone, -72%, $P<0.0005$; 15d-PGJ2, -88%, $P<0.0002$). [^{3}H]Leucine uptake was increased by 4% mechanical strain (1.9 ± 0.2 fold versus control, $P<0.002$), and this increase was inhibited by troglitazone and 15d-PGJ2 in a concentration-dependent manner (troglitazone, -52% at 10 μM, $P<0.01$; 15d-PGJ2, -70% at 10 μM, $P<0.005$). Total cell protein was also increased by 4% mechanical strain (control, 164.3 ± 11.9 mg/dish; strain, 265.5 ± 18.0, $P<0.0002$), and this effect was inhibited by troglitazone and 15d-PGJ2 (troglitazone, -61%, $P<0.005$; 15d-PGJ2, -72%, $P<0.001$). In addition, mechanical strain induced mRNA expression for brain natriuretic peptide, but both PPAR gamma activators inhibited this effect. Furthermore, both PPAR gamma activators inhibited the activation of nuclear factor-kB (NF-kB) induced by mechanical strain. Pyrrolidine dithiocarbamate, an inhibitor of NF-kB activation, inhibited strain-induced [^{3}H]leucine uptake (-50% at 100 μM, $P<0.05$).
Conclusions: These results demonstrate that PPAR gamma activators inhibit mechanically-induced cardiac hypertrophy in cardiac myocytes and suggest that PPAR gamma activators may regulate cardiomyocyte hypertrophy via the NF-kB pathway.

P1532 Superoxide production by left ventricular myocytes in control and hypertrophied hearts

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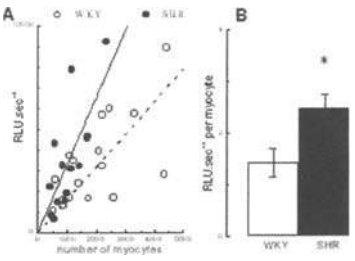
Oxidative stress induced by an increase in vascular superoxide anion (O2-) production has been implicated in the pathogeneses of cardiac hypertrophy and failure. However it is unknown whether O2- is generated from within ventricular myocytes themselves and whether an increase in its production is an early feature of myocardial pathology. In this study we have measured NADPH-stimulate O2- production in left ventricular myocytes isolated from age matched (8 week) Wistar (WKY) and spontaneously hypertensive rats (SHR) rats, using lucigenin-enhanced chemiluminescence (5μM lucigenin), at 37°C. Data are presented as mean±sem (n). NADPH elicited O2- production in a dose-dependent manner (EC50; 53±1 μM). NADPH-stimulated O2- production was not attenuated in myocytes pre-incubated with oxypurinol (100μM) or rotenone (100μM) but was abolished by the flavoprotein-oxidase inhibitor diphenyleneiodonium (100μM) and was quenched by tiron. Fig.1A shows that the relationship between NADPH-stimulated O2- production and myocyte number is steeper in hypertrophied (SHR) than in control (WKY) myocytes ($P < 0.05$). Mean data for the slope (calculated for each experiment) shows that NADPH-stimulated O2- production is increased by ~58% in hypertrophy from 1.43±0.27 in WKY to 2.46±0.28 RLU sec^{-1} per myocyte in SHR ($P < 0.05$, Fig 1B). Qualitatively similar data were obtained in a murine model of isoprenaline induced-hypertrophy.



Superoxide production in hypertrophy.

Conclusion: These data show for the first time that superoxide is released from within rat ventricular myocytes. NADPH-stimulated O2- production is mediated via a flavoprotein-containing oxidase (presumably NAD(P)H-oxidase) and is increased in hypertrophy. These findings suggest a putative autocrine role for superoxide in the control of cardiac function.

P1533 FKBP12 overexpression in isolated rabbit cardiomyocytes enhances intracellular Ca^{2+} transients, SR Ca^{2+} content and contractility

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In heart failure, Ca^{2+} release from the sarcoplasmic reticulum (SR) is disturbed. The FK506 binding proteins FKBP12 and FKBP12.6 coordinate function of SR Ca^{2+}-release channels (RyR) in striated muscle. FKBP12.6 binds to the cardiac RyR isoform (RyR2) and over-expression of FKBP12.6 in cardiac myocytes diminishes Ca^{2+} leak via RyR2, increases SR Ca^{2+} content and contractility. Expression levels of FKBP12 in heart are considerably higher than FKBP12.6, yet previous work suggested that FKBP12 does not associate significantly with RyR2. To investigate this further, we have enhanced FKBP12 expression in isolated rabbit cardiomyocytes using adenoviral gene transfer.
Successful overexpression was demonstrated by increased FKBP12 RNA, and -protein levels using RT-PCR and Western blots. Contractility of isolated rabbit cardiomyocytes was measured by video edge detection 48h post adenoviral transfection. When compared to lacZ transfected myocytes (beta-galactosidase control), FKBP12 over-expressing cardiomyocytes showed significantly increased fractional shortening (FS) (by 12%) at a multiplicity of viral infection (MOI) of 100 (2.1±0.2% vs 2.4±0.3%, respectively, n=12, p=0.04). In separate experiments, intracellular Ca^{2+} transients were monitored in Fura-2 loaded cardiomyocytes stimulated at 1Hz. No change in diastolic [Ca^{2+}] was observed in the two experimental groups, but peak systolic [Ca^{2+}] was significantly higher in FKBP12 over-expressing cardiomyocytes (587±25nM) compared to the lacZ control (482±28nM) group. Furthermore, the amplitude of the Ca^{2+} transient in response to 10mM caffeine was enhanced to a similar extent (peak value 1181±44nM vs 1003±50nM) indicating the increased contractility is a result of enhanced SR Ca^{2+} content.
Additional experiments were carried out on beta-escin permeabilised cardiomyocytes perfused with 160nM Ca^{2+} in a mock intracellular solution. Under these conditions caffeine-induced Ca^{2+} release was significantly greater in FKBP12 over-expressing cardiomyocytes when compared to lacZ transfected cells (caffeine integral = 0.7±0.1 μMs vs 1.6±0.1 μMs). This suggests that increased SR content in response to FKBP12 over-expression is a result of direct effects on cardiac SR function and challenges the current view, that FKBP12.6 is the isoform that exclusively modulates RyR2.

P1534 Mutations in the human muscle LIM protein gene in families with hypertrophic cardiomyopathy

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Introduction: Muscle LIM protein (MLP) is an essential nuclear regulator of myogenic differentiation. Additionally, it may act as an integrator of protein assembly of the actin-based cytoskeleton. MLP-knockout mice develop a marked cardiac hypertrophy reaction and dilated cardiomyopathy. MLP is therefore a candidate gene for heritable forms of hypertrophic (HCM) and dilated cardiomyopathy (DCM) in humans.
Methods: We evaluated 600 unrelated individuals (400 patients with DCM, 200 patients with HCM) using physical examination, ECG, echocardiography/TDI, and heart catheterization. DNA was extracted from blood. The samples were analyzed for mutations in the human CRP3 gene encoding MLP by polymerase chain reaction, single strand conformation polymorphism analysis, and sequencing.
Results: We found 3 different missense mutations in 3 unrelated patients with familial HCM, but detected no mutation in the DCM group and a control group (n=200). All mutations predict an amino acid exchange. They affect highly conserved residues in the functionally important LIM 1 domain which is responsible for interaction with alpha-actinin and with certain muscle specific transcription factors. Family studies revealed cosegregation of clinically affected individuals with the respective mutations in MLP.
Conclusion: Our study provides evidence that mutations in the CRP3/MLP gene can cause HCM.

P1535 Novel mutations in the beta myosin heavy chain (β-MHC) and myosin binding protein C (MYBPC3) gene are associated with dilated cardiomyopathy

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Mutations in the β-MHC and MYBPC3 gene have been reported to cause hypertrophic cardiomyopathy (HCM). Recently, mutations in the β-MHC gene and in the troponin T gene have been reported to cause dilated cardiomyopathy (DCM). In order to detect novel mutations in sarcomeric genes that are linked with DCM we screened the βMHC and the MYBPC gene in 46 consecutive patients with DCM.
Mutation screening was done with SSCP at 2 different temperatures. Comparison with the wave procedure in 1000 PCR fragments yielded >95% sensitivity for this approach. Mutations were confirmed by repeated sequencing of independent PCR products. The effect on proteins structure was determined with the STRAP: Editor for Structural Alignment of Proteins (Bioinformatics 2001:377) program.
In the β-MHC gene, the two mutations Ala 223 Thr and Ser 642 Leu were found in two young patients with severe DCM. They affect two highly conserved amino acids. Nonpolar side chains are exchanged against uncharged polar groups. The mutations are localized in the globular part (head) of the myosin molecule situated near the surface but not on the solvent accessible surface. Considering the effects of the mutants on the protein structure in comparison to all known 3-D-structures of myosin, including given sequence information, we conclude that both amino acid exchanges will influence the local structure.
In the MYBPC3 gene, Asn 948 Thr occurs in a DCM patient and exchanges a conserved AA. All three mutations were not found in 88 controls and not in 136 patients with HCM.
Thus, mutations in sarcomeric genes that are expected to modify protein structure and that have not been linked with HCM so far, are associated with DCM. Causal relations must be established by family studies.
Reference: Gille, C. und Frömmel, C. (2001). Strap: editor for structural alignments of proteins. Bioinformatics, 17, 377-378.

P1536 The human AT2 (+1675G/A) polymorphism influences left ventricular structure in hypertensive males, but not in females

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A polymorphism of the x-chromosomal human angiotensin II subtype 2 receptor (AT2-R) gene (+1675G/A) was recently associated with LV hypertrophy in young men with arterial hypertension, while in individuals without hypertension no such relationship was documented.
The aim of this study was to reinvestigate the implications of the AT2 +1675G/A polymorphism on LV structure in an independent population.
We used real-time PCR and melting curves on a LightCycler (Roche Molecular Biochemicals) to genotype the +1675G/A polymorphism of the human angiotensin II receptor subtype 2 in a total of 1534 participants of an age-stratified general population. LV hypertrophy was defined as a LV mass index (LVMI) of >=131 g/m^2 in men and >=100 g/m^2 in women and hypertension as a blood pressure >=160/100 mmHg. The overall frequency of the A and G allele was 57% and 43%, respectively. The slopes of the regression lines correlating systolic or diastolic blood pressure levels with septal thickness, posterior wall thickness and LVMI were significantly steeper in male individuals carrying the A-allele compared to the slopes in individuals with the G-allele ($p<0.01$). Moreover, septal wall thickness, posterior wall thickness and LVMI were significantly higher in hypertensive men carrying the A-allele as compared to those with the G-allele ($p<0.01$). In male hypertensive carriers of the A-allele prevalence of LV hypertrophy was substantially higher than in carriers of the G-allele (27.1% vs. 2.4%, $p<0.01$). In normotensive men and in women there was no association between LV hypertrophy and AT2 +1675G/A-polymorphism. Multivariate analysis confirmed the polymorphism as an independent predictor of cardiac hypertrophy related to pressure overload.
This study confirms the relation between the x-chromosomal AT2 +1675G/A-polymorphism and LV hypertrophy in hypertensive men. No such association could be demonstrated in women suggesting additional hormonal influences.

ATRIAL FIBRILLATION – ABLATION, MECHANISMS

P1537 Transveneous cryoablation of supraventricular tachycardia including atrial fibrillation

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Background: Radiofrequency (RF) catheter ablation is currently used in the treatment of cardiac arrhythmias. Although the success rate is high for almost all supraventricular tachycardias (SVT), this technique has some limitations in safety and effectiveness for treating more complex arrhythmias. The aim of this study is to report the acute safety and efficacy of a new cryoablation system when used for the treatment of SVT, including the treatment of atrial fibrillation (AF).
Methods: Forty-nine patients with SVT (age: 48 years; [23-76], male=38) were enrolled in this study. Five patients dropped out of the study prior cryoablation. The remaining 44 patients were treated with cryoablation (AF [n=22], atrial flutter [n=15], accessory pathway [n=3], AV nodal reentrant tachycardia [n=2], AV junction ablation for permanent AF [n=1], atrial tachycardia [n=1]). Cryoablation was performed with the CryoCor cryoablation system that uses a 10 Fr catheter, a pre-coolong system and N2O as the refrigerant. Acute success was defined as electrical block across the ablation site or line.
Results: The number of freezes applied varied according to the index arrhythmia treated (1-34 freezes/patient). Acute success was 100% (23/23) for right-sided procedures and 96% (20/21) for pulmonary vein isolation. Fifty-three out of fifty-five PV(s) were isolated (2.5 PV/patient). The case of failed PV isolation was complicated by persistent AF. The average and nadir catheter tip temperature for right and left-sided procedures were similar and stable -75±1.63°C and -80°C and -75±5.89°C and -78°C respectively. Procedure related complications included stroke (n=1), transient ST-T segment changes (n=1) and AV fistula (n=1). There were no serious cryoablation related complications or acute PV(s) stenosis.
Conclusions: This novel cryoablation system can safely and successfully treat various types of SVT including AF. Despite of the high blood flow in the right atrial isthmus and PVs, conduction block can be obtained at these sites with cryoablation.

P1538 Microwave isthmus ablation with a novel catheter

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Application of microwave energy, using different prototypes of generators and catheters (microwave antennas), has been considered more effective for the creation of transmural lesions than radiofrequency energy. The aim of the study was to test the safety and feasibility of creating linear lesions in the right atrial isthmus using a new microwave catheter. Also, the dose-response correlation of different energy settings on histopathological changes was studied. Ablation was performed in eight open chest mongrel dogs (weight: 29 ± 8 kg) using a 2.450 MHz microwave generator with 35-50 Watts and a recently designed 9 F deflectable catheter with a 25 mm antenna. Linear lesions were created at a mean maximum antenna temperature of 49 ± 3 °C. The catheter was placed first in the cavotricuspid isthmus and than withdrawn to the inferior vena cava until bidirectional block occurred. Bidirectional isthmus block was achieved in five dogs delivering 1.8 ± 0.8 (min: 1, max: 3) ablations. A total of eleven isthmus lesions were created, with a mean length of 12.9 ± 6.3 mm and width of 5.9 ± 2.4 mm. The histological examination of the lesions are characterized by haemorrhage, development of oedema, presence of focal fibrin thrombi in small vessels, focal myocytolysis or hypercontraction necrosis. None of the 4 lesions created by 35 watts were transmural, however 6 of the 7 lesions created by energy settings of 40-45-50 watts were transmural. Ventricular arrhythmias during energy delivery were not observed. Coronary artery thrombosis or significant catheter thrombosis were also not observed.

Conclusion: The lowest energy setting in this study (35 watts) was also able to produce acute bidirectional block, but the lesion was not transmural and characterized by oedema. This may be associated with a high recurrence rate. Low energy and insufficient tissue contact were probably responsible for the unsuccessful ablations. Based on these data, energy settings up to 40 watts (maximum 50 watts) and application duration of approx. 90 seconds are recommended.

P1539 The addition of a pre-cooler allows a novel catheter-based cryoablation system to obtain low and stable temperatures

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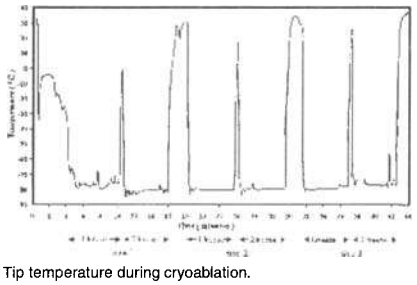
Background: Studies using cryothermia (Cryo) to create myocardial lesions have shown promising results. However, these earlier systems, when used for tranvenous ablation in regions of increased blood flow, may be underpowered to produce sufficient low and stable temperatures (T) needed to create permanent lesions. The study purpose was to evaluate a new cryoablation system that uses a pre-cooler to increase efficiency of catheter tip refrigeration.

Methods: The cryoablation system (CryoCor) consists of a 10-Fr catheter with a 6.5 mm tip electrode and a console. It uses a gas primary refrigerant that is pre-cooled (-35°C) to a liquid state by a secondary refrigerant. The primary refrigerant then expands through a small orifice at the catheter tip to produce the cooling effect. In 5 dogs right atrial isthmus (RAI) ablation was performed with Cryo to test the ability of the system to achieve and maintain adequate catheter tip T.

Results: All RAI were successfully ablated with 6 (see graphic) to 10 freezes at 3 to 5 sites. Nadir T was between -68 and -83°C (mean -75±1.6°C). T of -65°C was reached 3±0.2 sec and nadir T 9±0.5 sec after onset of Cryo. Mean T fluctuation during a freeze was 2.6±0.6°C.



Tip temperature during cryoablation.

Conclusion: The addition of a pre-cooler appears to overcome the issues associated with transvenous Cryo, namely the ability to achieve rapid, low and stable catheter tip T.

P1540 Atrial natriuretic peptide before and after cardioversion therapy in patients with chronic atrial fibrillation

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The treatment of patients (pts) with atrial fibrillation (AF) has improved significantly during the past decade, but most pts remain limited by symptoms and recurrence of arrhythmia. The studies on neurohormonal remodeling in pts with AF are becoming increasingly important. The results could possibly enhance treatment of these pts.

The aim of this study was to determine plasma atrial natriuretic peptide (ANP) concentrations in pts with chronic AF, one day before, the day after and 30 days after electrical cardioversion (CV) therapy.

Methods: We attempted CV in 42 consecutive pts (30 men and 12 women), aged 57±8 years, with chronic nonvalvular AF of duration 7±6 months. The underlying heart disease was diagnosed as systemic hypertension in 20, ischaemic heart disease in 17, dilated cardiomyopathy in 3 and arrhythmia alone in 2 pts. All these pts had good left ventricular function, with ejection fraction of >50%. They were in controlled AF and with normalized blood pressure. Plasma samples of ANP were obtained at rest: one day before, the day after and 30 days after CV therapy, and were prepared by refrigerated centrifugation and stored until radioimmunoassay.

Results: CV was successful in 35 pts. However in 6 of the 35 pts, AF reappeared within 1 month. The control group comprised 11 pts, matched with age, sex and concomitant diseases, and without AF. There were not statistical differences before CV in pt's characteristics between the group with successful CV and unsuccessful CV or with recurrence of AF. The mean baseline ANP level was 58,5±15,7 pg/ml in the study group and 34,3±10,2 pg/ml in the control group ($p<0,01$). The successful therapy reduced significantly the pretreatment mean plasma ANP concentration from 58,5±15,7 to 31,4±15,0 pg/ml; $p<0,01$, the day after CV, in the group of 35 pts. It remained stable for the next 30 days (36,9±15,2pg/ml) in the group of 29 pts who remained in sinus rhythm, and increased to 53,4±16,4pg/ml in the group of six pts who had recurrence of AF. Plasma ANP did not change in the group of 7 pts with unsuccessful CV, one day before, the day, and 30 days after CV: 60,2±10,7; 59,4±10,4; and 56,6±10,6 pg/ml, ns, respectively.

Conclusions: The plasma ANP concentration in pts with AF was significantly reduced after successful CV and remained stable for a period of 30 days.

P1541 Evaluation of atrial propagation by electroanatomic mapping in patients with idiopathic paroxysmal atrial fibrillation versus control patients

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The aim of this study is to evaluate atrial conduction in pts with idiopathic paroxysmal atrial fibrillation (IPAF) by comparing electroanatomic propagation maps on sinus rhythm of IPAF pts vs control (C) pts. After informed consent, 15 pts were included in the study; 8 (8 M, mean age 40±11 yrs) in the IPAF group and 7 (5M, 37±11 yrs) in the C group. In the IPAF group, pts had no frequent ectopies triggering AF episodes, no organic heart disease and they were on stable sinus rhythm and off drug at the time of evaluation. In the C group, pts had no history of atrial arrhythmias, no organic heart disease and underwent an off drug electrophysiologic procedure for ablation of a left-sided accessory pathway. Mapping was performed on stable sinus rhythm, in both atria, by an electroanatomic mapping system (CARTO, Biosense-Webster, Inc.). Qualitative and quantitative analyses of propagation maps were performed. A mean of 110±22 and 87±20 mapping sites were acquired in the right (RA) and left atrium (LA), respectively. The propagation duration was longer both in the RA (106±8 vs 92±10 ms) and in the LA (103±18 vs 81±10 ms) in IPAF pts as compared to C pts. Accordingly, also the atrial systolic time interval was longer in the IPAF group than in the C group (136±20 vs 105±9 ms, respectively). Particularly, a marked prolongation (mean value in the C group + 2 standard deviations) of propagation was observed in the RA in 3 pts and in the LA in 4 pts. In addition, 4 pts showed a marked prolongation of the interatrial propagation over the Bachmann's bundle. No prolonged propagation was observed in the C group.

In conclusion: these preliminary data show that a subset of pts with AF, even in the absence of an organic heart disease, have an altered atrial conduction on sinus rhythm, as compared to C pts. Electroanatomic mapping seems to be able to identify different pattern of altered propagation.

P1542 C-reactive protein and atrial fibrillation: evidence of an inflammatory process in the initiation and perpetuation of the arrhythmia

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Atrial Fibrillation (AF) is the most common sustained arrhythmia.The mechanisms that contribute to the triggering and perpetuation of AF are still not fully understood. We hypothesized that an inflammatory process can be involved in the genesis and maintenance of AF. We determined C-reactive protein (CRP), a marker of systemic inflammation, in patients with paroxysmal and chronic AF.
Methods and Results: We prospectively determined CRP plasma levels (immunoturbidimetric method) in 104 patients: 88 with non-valvular AF (50 with paroxysmal and 30 with chronic AF) and 16 patients with valvular heart disease, and compared them with 20 normal subjects in sinus rythm matched by age and sex. Mean age of the group was 66 ± 14 years old, 55 males. Forty-six percent of the patients were > 70 years old, 51% were hypertensives, 14% diabetics and 34% had associated CAD and/or dilated cardiomyophaty. Seven patients reported previous embolic events. Transesophageal echocardiography showed 56% of patients with an enlarged left atrium (>45 mm), 54% with left atrial echo contrast and/or presence of thrombus, and 12% with evidence of systolic left ventricular dysfunction. CRP levels at entry were 1.1 ± 1.9 mg/dL in the entire cohort, 0.6 ± 0.9 mg/dL in patients with paroxysmal AF, 1.7 ± 3.4 mg/dL in patients with chronic AF and 1.7 ± 2.1 mg/dL in patients with valvular AF. CRP levels were significantly higher in all groups when compared to a control group of 20 patients in sinus rythm (p = 0.001 entire AF, p = 0.01 paroxysmal AF, p =0.01 chronic AF and p = 0.03 valvular AF versus controls). Overall, there was a trend for reduction in CRP levels after 30 days (p = 0.06). The reduction was significant and more pronounced in patients with chronic AF than paroxysmal AF (p = 0.03) and it was not related to use of antiplatelet and/or oral anticoagulants agents after discharge or during the 30-day follow up. CRP levels were significantly related to history of hypertension (p = 0.03) and left atrial enlargement (p = 0.04) but not to age (p = 0.98).
Conclusions: This study provides evidence of the presence of an inflammatory process that may be involved in the genesis and perpetuation of AF.

P1543 Characterization of paroxysmal and persistent atrial fibrillation in the human left atrium

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Atrial fibrillation (AF) in the left atrium (LA) is poorly defined in terms of regional differences in the degree of organization.
Methods and Results: The study population consisted of 21 patients (15 men and 6 women; mean age 58 ± 9.4 years) with paroxysmal (10 patients) and persistent (11 patients) AF. Mapping of the LA during AF was performed with a 64-electrode basket catheter (Constellation® Boston Scientific) equipped with a software to perform quantitative analysis of AF characteristics. Patients with paroxysmal AF had longer AF cycle lengths (CL) and more pronounced regional differences as compared with the patients with persistent AF. A septal-to-lateral gradient in the distribution of the AF CL, with the septal region showing the shortest CL was observed. In total, AF CL in the LA in patients with persistent AF were 20% shorter than in patients with paroxysmal AF. AF CL in the coronary sinus (CS) were 21% shorter in patients with persistent as compared with patients with paroxysmal AF.
Compared with CL in the posterior wall of the LA, the CS CL were 26% and 29% longer in patients with paroxysmal and persistent AF, respectively. Type I AF was dominant pattern in the anterior wall of the LA. In all other regions of the LA in the paroxysmal and persistent AF groups the type III AF was the most dominant pattern in the activation of the LA. The CS activation displayed a higher degree of organization as compared to the posterior wall of the LA.
Conclusions: AF in the LA displays substantial regional differences in terms of AF cycle lengths and the degree of organization (types of AF). Patients with persistent AF have shorter cycle lengths and a higher degree of disorganized activity than patients with paroxysmal AF. Due to substantial differences in terms of AF cycle lengths and the activation patterns, the CS does not reflect the LA activity.

P1544 Upregulation of the atrial Na/Ca-exchanger in patients with atrial fibrillation: correlation with atrial pressure and the degree of heart failure

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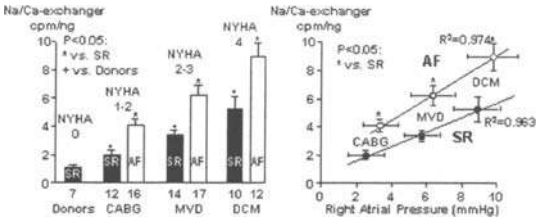
Background: Altered Ca^{2+} homeostasis has been hypothesized to contribute to the proarrhythmogenic substrate in atria of patients with atrial fibrillation (AF). Increased likelihood of delayed after-depolarisations (DADs) mediated by the Na^{+}/Ca^{2+}-exchanger (NCX) might contribute to this phenomenon. We studied the NCX protein expression in right atria of patients with and without AF.
Methods: Using Western blot analysis we determined the protein expression of the NCX in right atrial appendages of 88 patients. 7 Appendages were obtained from organ donors, the other patients underwent: coronary artery bypass graft surgery (CABG, n=28), mitral valve surgery (MVD, n= 31), or cardiac transplantation due to dilated cardiomyopathy (DCM, n=22). The atrial NCX content was related to the atrial rhythm and to the hemodynamic and clinical state of the patients.
Results: In all underlying heart diseases the NCX was significantly upregulated in patients with AF. In addition, a higher NYHA class and an increased atrial pressure were associated with an upregulation of the NCX.



NCX protein expression in right atria.

Conclusion: The high prevalence of AF in patients with a higher NYHA-class suggests that an increased probability for DADs due to the upregulation of the NCX might contribute to the proarrhythmogenic substrate in AF.

P1545 Right and left atrial initiation of atrial fibrillation: three-dimensional atrial activation analysis

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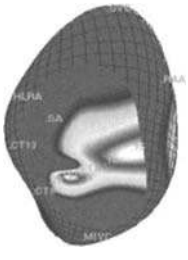
The origin of atrial premature beats (APBs) and onset of spontaneous AF was studied with 3-D non-contact and biatrial catheter mapping in 36 pts with recurrent, drug-resistant AF: Gp.1 - 16 pts had focal pulmonary vein (PV) or left atrial (LA) triggers and Gp.2 - 20 pts had right atrial (RA) triggers. In all pts RA or LA AF was initiated by a single beat-to-beat changing wavefront. In Gp.1 the mean AF cycle length (CL) was 211±34 ms. In 10 Gp. 1 pts, a single LA wavefront emerged into the RA in the high (n=4) or mid septum (n=6) and divided into superior and septal RA wavelets (Fig.1). The superior wavelet activated the lateral RA and the septal wavelet propagated craniocaudally and transversely to fuse with the superior wavelet. In 6 Gp.1 pts, inferior septal breakthrough was followed by caudocranial activation with a single RA wavefront. Mean RA activation time in Gp.1 was 171±40 ms, with electrical quiescence present between successive AF cycles. In Gp.2 the mean AF CL was 239±41 ms, (p=.11 vs Gp.1). APBs initiated a single macroreentrant wavefront without electrical quiescence between AF cycles, resulting in 2 or 3 daughter wavelets in 13 pts (p=.10 vs Gp.1).



Conclusions: 1. Dynamic macroreentrant tachyarrhythmia initiated by focal trigger precedes sustained AF in both atria. 2. Single septal breakthrough wavefront and up to 2 daughters RA wavelets activates RA in LA onset of AF. 3. Continuous RA activation due to a single dynamic macroreentrant wavefront often resulting in 2 or 3 daughter wavelets features RA onset of AF.

P1546 Induction of apoptosis in atrial and Bcl-2 upregulation in ventricular myocytes is a transient phenomenon in persistent atrial fibrillation

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Background: The cellular changes from electrical to structural remodeling in persistent atrial fibrillation (AF) are not all known.
Methods: Myocardial samples were obtained from the hearts of 44 goats which had undergone cardiac pacemaker (660ppm) implantation to induce AF in 31 goats for 2 to 430 days. Cardiac samples from the other 13 goats in sinus rhythm (SR) were used as controls. Apoptosis was evaluated histo- and biochemically.
Results: Persistent AF for 3 months was characterized morphologically by an up to 9-fold increase in atrial myocyte apoptosis (TUNEL staining, 0.27 ± 0.05% vs. 0.03% ± 0.01%, $p<0.001$) and biochemically by agarose gel electrophoresis and Western blots for Bax, Bcl2, Cytochrome C, activated Caspase-3(p20); the percentage of ventricular myocytes labeled with Bcl2 was 5-times higher for goats in AF than in SR ($p<0.005$). The percentage of apoptotic atrial myocytes, but not fibrocytes, correlated with the duration of AF ($p<0.05$). After peaks of apoptotic myocytes, atrial volume increased. Patchy fibrosis in the atrial wall (13±2% after 430 days) correlated with the duration of AF ($p<0.05$). Glycogen accumulated in atrial myocytes over time. Goats in AF for 430 days revealed apoptosis in atrial and Bcl2 expression in ventricular myocytes comparable to baseline levels (ns.).
Conclusions: In this model, programmed death of myocytes increases within 60 to 180 days of AF, despite enhanced Bcl2 expression and prior to atrial stretch and fibrosis. After 230 to 430 days the extent of apoptotic myocytes in goats with AF is indifferent to SR. This transient phenomenon may contribute to the progression of electrical and structural remodeling associated with AF.

P1547 Intraoperative radiofrequency ablation of atrial fibrillation (IRAAF) study stopped after 386 pts. treated because of significant complications

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Since July 1997 intraoperative radiofrequency ablation (IRAAF) of atrial fibrillation (AF) was performed in 387 patients (pts.; 237 men, 150 women, mean age 61 ± 10 yrs.) with paroxysmal (26%) or permanent (74%) AF. In all pts., contiguous left atrial (LA) lesion lines between the mitral annulus and the pulomonary veins were induced temperature-guided (60°C, unipolar energy application) with a hand-held ablation probe (Osypka). 129 pts. underwent the procedure exclusively for the treatment of AF while in the other pts. IRAAF was performed in combination with mitral valve surgery (163 pts.) or various other types of heart surgery (95 pts.). Damage of the oesophagus following the procedure was observed in 4 pts. (1%). The first pt. (no. 56) with this type of complication developed fever and recurrent neurological symptoms 5 days after surgery. Re-operation revealed perforation of the oesophagus and an fistula to the left atrium resulting in air embolism. Initially, it was believed that the complication was due to mechanical perforation of the oesophagus by a transoesophageal echo probe. However, the intraoperative treatment concept was also slightly changed: The lesion line between the left upper and right upper PV was deployed more superior along the roof of the LA instead of posterior. However, damage of the oesophagus occurred in 2 additional pts. (nos. 239 and 241). Histological analysis of the oesophageal lesion showed thermal damage of the tissue thus proving direct effects of radiofrequency ablation. Prevention of thermal damage of the oesophagus was then attempted by careful intraoperative surgical separation of the oesophagus from the left atrium and by placement of a isolation scrub into the Sinus obliquus pericardii. However, although all preventive efforts were made, perforation of the oesophagus occurred in an additional patient (no. 382). This pt. also had to undergo surgical repair of the oesophagus.
Conclusions: Intraoperative induction of linear lesions to the left atrium bears the risk of severe damage of the oesophagus. Although this complication occurred rarely (1%), the IRAAF program was stopped because no effective prevention seems to be possible when radiofrequency is applied to the endocardium in unipolar fashion. This type of complications may also occur following percutaneous left atrial ablation.

P1548 Safety and efficacy of antiarrhythmic surgery using cooled-tip radiofrequency ablation in patiens with chronic atrial fibrillation

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The original Cox-Maze procedure is a highly effective method to restore Sinusrhythm (SR) even in patients with chronic atrial fibrillation (AF). Is a method applying intraoperatively linear lesions using cooled-tip radiofrequency (RF) ablation effective and safe in treating chronic permanent AF in patients undergoing open heart surgery?
Method: 93 patients (mean age 67 years, mean ejection fraction 61%, left atrium 53mm diameter)) with chronic permanent AF (mean duration 54 months) underwent open heart surgery (mitral valve replacement in 35, mitral valve plasty in 12, coronary artery bypass in 22, aortic valve replacement in 10 and combined procedures in 14) plus an additional modified maze procedure using intraoperatively cooled tip RF ablation.
Results: The mean extracorporal circulation duration was 168 minutes and the cross-clamp time was 101 minutes. The 30-day mortality was 2.1% (2/93). After a mean follow-up duration of 15 months a cumulative rate of SR of 0.77 was documented. Mode of conversion to SR was spontaneous in all but 1 patient usually within the first 6 months after the procedure. Doppler-echocardiography 6 months after the procedure revealed (43 patients) biatrial contraction in 85%, right atrial contraction in 13% and no atrial contraction in 2% of patients in SR. Conclsions: Antiarrhythmic surgery using intraoperatively cooled-tip RF ablation is a safe and effective method to treat chronic permanent AF in patients undergoing open heart surgery. SR can be restored in 77% of patients with variable indication for cardiac surgery and biatrial contraction can be documented in 85% of these patients.

P1549 Tissue temperature controlled radiofrequency ablation

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Background: During radiofrequency energy delivery catheter tip temperature can be significantly lower than tissue temperature. We performed tissue temperature controlled radiofrequency ablation in vitro and evaluated the effects of cooling, electrode-tissue contact and target tissue temperature on lesion size.
Methods: Pieces of porcine ventricle were immersed in a bath of isotonic saline solution at 37° C. Radiofrequency energy was controlled by the tissue temperature as measured with a thermocouple needle placed 2 mm beneath the ablation electrode. Radiofrequency power was delivered for 30 seconds and limited to 50 W. A total of 81 radiofrequency ablations was performed with different electrode-tissue contact forces (0.04 N, 0.36 N and 0.67 N) and target tissue temperatures (50°C, 60°C and 70°C) using either an irrigated (27 ablations, 20ml/min irrigation flow rate) or a non-irrigated ablation catheter. Twenty-seven non-irrigated applications were performed with fluid flow maintained by the pump of the thermostat and another 27 applications without flow. Every combination was applied 3 times and the average values were used for evaluation.
Results: For tissue target temperatures of 50° C, 60° C and 70° C the lesion volume for non-irrigated ablations was on average 21 ± 8 mm^3, 45 ± 23 mm^3 and 109 ± 45 mm^3, respectively, requiring an average power of 6 ± 2 W, 10 ± 5 W and 20 ± 9 W, respectively, to reach target tissue temperature. For irrigated ablations the respective values for lesion volume were 12 ± 7 mm^3, 37 ± 20 mm^3 and 92 ± 30 mm^3, respectively, with an average power of 8 ± 2 W, 10 ± 3 W and 19 ± 9 W, respectively. The lesion size was in both application groups not correlated to the electrode-tissue contact force. In the non-irrigated ablation group the catheter tip temperature was on average 66 ± 13° C in the group with fluid flow and 83 ± 13° C in the group without flow whereas the tip temperature in the irrigated group was 33 ± 1° C on average. There was no difference in lesion size between the group with fluid flow and those without.
Conclusion: Lesion size during tissue temperature controlled radiofrequency delivery increases with increasing target tissue temperature and becomes independent of flow and electrode-tissue contact. Irrigation of the catheter tip electrode does not increase lesion size but avoids excessive heating of the ablation electrode. Our data suggests that a cooled tip ablation catheter with an extractable needle allowing for tissue temperature controlled ablation may yield reproducible and predictable lesions.

ATRIAL ARRHYTHMIAS

P1550 Origin of electrical activation within the right atrial wall: differentiation by electrogram characteristics using non-conact mapping

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Background: Clinical data using the non-contact mapping system (Ensite 3000) in mapping and ablation of atrial ectopic tachycardia suggest that characteristics of reconstructed unipolar electrograms may predict the origin of electrical activation within the atrial wall (endocardial vs. myocardial vs. epicardial origin).
Animals and Methods: In ten pigs (mean body weight 62 kg) pacing (600 msec, 2 msec, double diastolic threshold) was performed at the lateral high right atrium, at the mid-posterior right atrium and at the lateral inferior right atrium from the endocardium, the myocardium and the epicardium, respectively. Activation was recorded using the non-contact mapping system. Reconstructed unipolar electrograms at the location of earliest endocardial activation assessed by isopotential maps were analysed systematically for differences in morphology.
Results: see table.

Pacing site	max. V	dV/dt	Initial R-wave
Endocardial	-1.95±1.03 mV	377.5±250.7 mV/ms	5%
Myocardial	-3.04±1.84 mV	798.22±860.4 mV/ms	56%
Epicardial	-2.08±0.67 mV	440.8±401.6 mV/ms	58.3%
p	<0.01	<0.01	<0.001

Presence of initial R-wave had a positive predictive value of a subendocardial origin of electrical activation of 0.96. In addition, unipolar electrograms during myocardial stimulation exhibited significantly higher max. voltage and a more rapid dV/dt.
Conclusions: Morphology characteristics of unipolar electrograms generated by non-contact mapping allow for discrimination of an endocardial versus an subendocardial origin of atrial activation. Findings may be helpful in selecting the appropriate mode of energy delivery during ablation procedures.

P1551 Upstream stimulation versus downstream stimulation: arrhythmogenesis based on repolarization dispersion in the human heart

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Background: Induction of sustained ventricular tachycardia (VT) is often feasible at one stimulation site while application of an identical pacing protocol to another site fails to provoke VT. We tested the hypothesis that a dominant VT induction site has shorter action potential duration (APD) and effective refractory period (ERP) than a non-inducing site, resulting in collision against longer ERP ("upstream") as opposed to shorter ERP ("downstream", no collision).
Methods: Sixty-nine patients undergoing programmed stimulation for VT inducibility had monophasic action potential recording/pacing catheters placed in the right ventricular outflow tract (RVOT) and apex (RVA) simultaneously. At basic cycle lengths of 600ms and 400ms, up to 3 extrastimuli were introduced in 5-10ms decrements until ERP was reached. Upon completion of a drive cycle at one stimulation site, it was repeated at the other site. A drive train that induced VT was compared to a corresponding train at the other stimulation site.
Results: Thirty-eight patients had inducible VT, 9 exclusively by RVA pacing and 9 exclusively by RVOT pacing. APD and ERP at the induction site were significantly shorter (12±15ms, $p<0.05$ and 22±14ms, $p<0.01$, respectively, at 600ms BCL) than at the non-induction site. The dispersion of repolarization between corresponding action potentials at the two sites was 58±41ms during baseline stimulation (S1) at the inducing site but only 37±23ms at the non-inducing site ($p<0.05$). Extrastimulus application increased the dispersion of repolarization at both sites ($p<0.05$). Dispersion reached a maximum of 75±45ms during VT induction, but only 53±33ms during extrastimulation at the non-induction site ($p<0.05$ for intersite difference).
Conclusions: Site specificity of VT induction underscores the role of dispersion of repolarization and refractoriness in facilitating reentry arrhythmias. Upstream stimulation at a site with short repolarization produces larger dispersion and facilitates VT induction.

P1552 Resynchronization of atrial compartments after catheter maze with dual-site right atrial pacing

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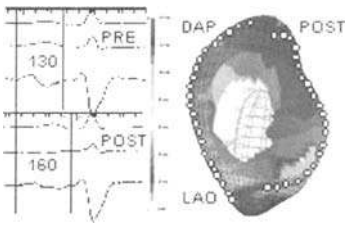
Catheter right atrial (RA) maze procedure may be more effective in combination with dual site RA pacing (DAP). We analyzed P wave duration before and after RA maze in 30 pts with refractory AF and in a subgroup (n=20) undergoing DAP after RA maze. 3-D non-contact mapping (NCM) was employed to analyze RA activation patterns. Results: 30 pts, mean age 69±10 yrs, mean LA size 42±9 mm, mean LVEF 43±12%, with cardiac disease (n=25) were studied. NCM showed effectiveness of RA maze in all pts with distinct lines of intraatrial block with anterior and posterior RA compartments. Prolonged atrial activation in individual RA compartments was noted in all pts immediately after the procedure. Mean P wave duration was 139±19 ms before RA maze and increased to 161±24 ms after it ($p<.001$). P wave amplitude was also significantly reduced. Intraatrial reentrant tachycardias circulating around the linear lesions or within a RA compartment were seen in 7 pts (23%). DAP produced two distinct, simultaneous wavefronts in each RA compartment resynchronizing them and reducing P wave duration to 136±16 ms ($p<.001$). Global atrial activation time was reduced by 10-30% (mean 18%).



ECG pre/post & isochrones of DAP post.

Conclusions: 1. RA maze significantly prolongs global biatrial activation time and can promote macroreentrant arrhythmias in the atrium. 2. Antiarrhythmic benefit of DAP after RA maze can be due to resynchronization of atrial compartments, as well as collision of simultaneously paced wavefronts on both sides of linear lesions.

P1553 Radiofrequency ablation of atrial arrhythmias after a remote open-heart surgery: role of conventional and CARTO mapping

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Background: Considering the complex nature of the substrate after open-heart surgery, conventional mapping for radiofrequency (RF) ablation of atrial arrhythmias (AA) could be supplemented by CARTO electroanatomical mapping.
Methods: Mapping and RF ablation was performed in 19 patients (50±11 years, 11 women) having symptomatic AAs after a remote open-heart surgery: valvular (n=8), atrial septal defect (n=9), Ebstein's(n=1) and Rastelli's (n=1) repair. Only conventional mapping [peri-tricuspid (PT) Halo, His and coronary sinus catheters] was performed in 11 patients. CARTO was done, de novo (n=4) or for the same (n=2)/a new (n=2) recurrent AA after previous RF ablation, in the remaining 8 patients and as supplementary to conventional mapping.
Results: Linear ablation of the low right atrial (RA) isthmus for PT atrial flutter (AFL): counterclockwise (n=7), clockwise (n=2), and previously documented (n=1), was successful after conventional mapping alone in 10 patients (91%). Conventional mapping failed to localize the AA and ablation was unsuccessful in the remaining 1 patient. Activation maps generated using the CARTO system showed, a clockwise PT (n=2), septal (n=2) and a double-loop (n=1) reentry in 5 patients. The AA cycle length was mapped almost completely (92%±11%). A voltage (scar) map alone could be obtained during sinus rhythm in 2 other patients. Conventional mapping had shown PT-AFL in these patients. An unconventional isthmus, between the scar and an anatomical barrier (superior/inferior vena cava or tricuspid annulus), was ablated more often (n=5) then the low RA isthmus (n=2). The ablated isthmus was anatomically the most convenient (2.7±1 cm), but not the slowest conducting zone. Two focal atrial tachycardias were seen in the remaining 1 patient. Ablation was successful in all 8 patients (100%), although after a second CARTO procedure in 1 patient. After a follow-up of 12±11 months, 2/18 patients (11%) ablated successfully had a same (1) or a new (1) AA recurrence.
Conclusions: AAs after a remote open-heart surgery can be ablated successfully (>90%) with a low recurrence rate (11%). Despite an underlying scarred substrate, PT-flutter circuits were frequent (72%). These could be mapped and ablated successfully using conventional techniques. CARTO mapping helps to uncover peri-scar reentry and guide ablation of unconventional isthmi.

P1554 Use of CARTO to identify the critical isthmus in left atrial macroreentrant tachycardia and to guide successful ablation

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Right atrial macroreentrant tachycardia can be ablated with high success rates. However, left atrial macroreentrant tachycardia (LAMRT) are less well understood and ablation success is limited. We therefore investigated 19 pts (6 with normal hearts and 13 with structural heart disease but none with left atriotomy) with permanent left atrial macroreentrant tachycardia (LAMRT; cycle length 325±89 msec; range 205 to 510 msec).

Methods and Results: CARTO maps of the LA were performed during LAMRT in all pts (223±50 points/map; range 115 to 345) and identified 1-4 electrical silent areas or lines of double potentials per patient. In 16 pts 25 LAMRT circuits (CL>=240 msec) were identified as single loops (n=6) or dual loops (n=19) with the reentry propagating through an isthmus located between a PV and a posterior electrical silent area/ line of double potentials (n= 6), anterior electrical silent area/ line of double potentials (n=4) or roof line of double potentials (n=1), between the mitral anulus and an anterior electrical silent area/ line of double potentials (n=5), between two distinct anterior electrical silent areas/ lines of double potentials (n=6), between two roof electrical silent areas (n=2), or between a posterior and a roof electrical silent area (n=1). Ablation targeted an isthmus-width of 10.8±4.6 mm (range 4.0-21.6 mm) and maximal bipolar atrial amplitude of 0.04-1.22 mV. A mean of 3.3±1.8 radiofrequency (RF) applications resulted in termination of the LAMRT and conduction block across the identified isthmus in 16/16 pts. In contrast, the LAMRT circuit could not be identified in the remaining 3 pts with faster LAMRT (CL<=230 msec) due to multiple electrical silent areas/ lines of double potentials or inability to identify >90% of the reentry cycle length. During a mean follow-up of 1-31 months (median 15 months) LAMRT recurred only in 2/3 pts with failed ablation, while atrial fibrillation occurred in 3/16 pts in the successfully treated group and in 1/3 pts in the failed ablation group.

Conclusions: High density mapping using CARTO can identify the reentrant circuit in LAMRT. The location of the critical isthmus is variable, but usually narrow and of low amplitude. Conduction block across the left atrial critical isthmus can be achieved with few conventional RF applications resulting in high success and low recurrence rates.

P1555 Feasibility of catheter cryoablation for ablation of atrioventricular nodal reentrant tachycardia and complete atrioventricular junction ablation

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Background: Nowadays radiofrequency ablation is the standard procedure for the ablation of tachycardias. In this study experiences with the recently developed catheter cryoablation are reported in patients with AV nodal reentrant tachycardia (AVNRT) and for the complete AV junction ablation.

Methods: Cryoablation was applied to 26 patients, 20 with AVNRT. In 6 patients with atrial fibrillation a complete AV junction ablation was carried out. The CCT.2 CryoConsole by CryoCath® and the Cardiac CryoAblation Catheters Freezor® 3 and Freezor® 5 by the same company were used for ablation. In all cases a cryomapping with a temperature of - 30°C preceded the cryoablation with the temperature of - 75°C. During the cryoablation each application lasted 240 seconds.

Results: Acute success could be obtained in 18/20 patients with AVNRT. In two patients the effect on the slow pathway was only temporary, so that the ablation had to be finished with radiofrequency energy. In another patient a reversible third degree AV block was observed. In one of the 6 patients with complete AV junction ablation a complete AV block could not be achieved, so that the ablation had to be continued with radiofrequency energy. In another patient a second procedure with radiofrequency energy had to be carried out because of a recovery of AV nodal conduction. Especially in patients with AVNRT and running tachycardia cryomapping was useful for confirmation of a successful ablation site. Another advantage of cryoablation is the stability of the catheter position due to freezing of the tip.

Conclussion: Cryoablation is a promising alternative to radiofrequency energy in the ablation of tachycardias, which so far has been applied in patients with AVNRT and for complete AV junction ablation in our institution. A cryomapping is useful to find a successful ablation site. Another advantage is the stable catheter position due to freezing of the catheter tip.

P1556 Percutaneous cryoablation of antero-septal and mid-septal accessory pathways: a step-by-step method

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Recently, percutaneous cryoablation (Cryo) has become available for ablation of cardiac arrhythmias. This study describes a method for Cryo of accessory pathways (APs) close to the normal atrioventricular conduction system, such as antero-septal and mid-septal APs. To this aim, 7 pts (6 M, mean age 29±8 yrs) were considered: 3 had a para-hissian, 2 an anterior para-septal and 2 a mid-septal AP. In all pts a novel catheter for Cryo (Freezor 3, Cryocath Technologies, Inc.) was used, in which the cooling effect of the tip electrode is obtained by expansion of fluid N2O. Ablation was performed in sinus rhythm (4 pts) or AV reentrant tachycardia (3 pts), according to the following protocol: 1) the most suitable site was selected during mapping in sinus rhythm and/or tachycardia; 2) the firmest tissue/electrode contact was obtained by switching from the inferior to the superior vena cava approach, if necessary; 3) test applications were performed for 30 s with a progressive step-by-step decrease in the tip electrode temperature from -30 to -75°C until AP conduction interruption was observed; then, after further check for 20 s at the effective temperature, Cryo application was performed at -75°C up to 120-240 s (para-hissian and mid-septal APs) or 240-480 s (anterior para-septal APs). At any moment during cooling, if any sign of initial modification of conduction over the normal pathway (minimal A-H interval prolongation, appearance of right bundle branch block, termination of orthodromic AV reentrant tachycardia in the antegrade limb) occurred, cryo had to be immediately interrupted. The test application interrupted AP conduction at -33±28°C (range 0 to -75°C) and Cryo was then continued according to the protocol for 251±167 s (range 40-480 s). Due to cryoadherence effect, the catheter never displaced during cooling, even when sudden changes in heart rhythm occurred. In 2 pts, an initial modification of the conduction over the normal pathway (15% A-H interval prolongation in one case and right bundle branch block in another) was observed after 170 and 40 s and at -75 and -40° C, respectively; these modifications rapidly reverted upon Cryo discontinuation. In all pts the procedure was successful with no complication; no pt had recurrence in a 115±42 day (range 210-90 days) follow-up.

In conclusion: a step-by-step method for Cryo of antero-septal and mid-septal APs is permanently effective and safe; initial modifications over the normal condution pathway are reversible, if Cryo is timely interrupted; cryoadherence contributes to safety in this critical area.

P1557 Unusual variants of accessory pathways with wide-ranging atrial and ventricular insertions: successful linear ablation within the coronary sinus

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Accessory atrioventricular (AV) pathways are usually described electrophysiologically and histologically as discrete cable-like muscle fibers with some degree of terminal ramification. In many cases, singular energy applications are sufficient for successful ablation.

In 3 young patients (pts) (age; 4, 14, and 18 years, respectively) with recurrent atrioventricular reentrant tachycardia (AVRT), invasive electrophysiologic testing was performed. In all cases, exclusively retrograde conduction over the accessory pathways was present. Coronary sinus mapping during AVRT revealed earliest retrograde atrial activation at the left inferior mitral annulus in all pts. However, in one case, spontaneously changing activation sequences were observed left inferior, and in the other 2 cases, earliest retrograde atrial activation was recorded over a range of coronary sinus electrodes. Repetitive energy applications to the presumed atrial and ventricular insertion sites were unsuccessful in all cases. The recording of unusually big accessory pathway activation potentials within the coronary sinus then led to ablation within the coronary sinus. Step by step ablation within the coronary sinus, thereby placing a linear lesion, allowed successful ablation in all cases. Coronary sinus ablation was started left inferior, and in 2 cases, the final energy applications were done in the coronary sinus ostium. In the remaining case, the accessory pathway network extended to the right side and ablation was continued to the right inferior area at the tricuspid annulus. Coronary sinus angiography revealed normal findings in all pts. No complications were observed.

In rare cases of young pts with accessory pathways, wide-ranging ventricular insertions can be observed extending from the left inferior mitral annulus to the coronary sinus ostium or even to the right inferior tricuspid annulus. Placement of linear lesions within the coronary sinus allows successful ablation of these unusual accessory pathways along their left sided course extending towards the coronary sinus ostium.

P1558 Transcutaneous epicardial radiofrequency ablation for treatment of posteroseptal accessory pathways not achievable via the middle cardiac vein

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Although radiofrequency ablation (RFA) provides complete cure for nearly all patients with accessory pathways (APs), epicardial course has been clearly recognized as a possible cause of the prolonged or failed attempts.
Methods: A 57-year-old man presented with palpitations followed by syncope and sudden cardiac death. His first ECG showed a pre-excited atrial fibrillation (AFib), with shortest RR interval of 210 msec. Clinic evaluation was unremarkable. After 3-failed endocardial ablation procedures was attempted, and being refractory to medical therapy, he underwent to epicardial ablation. Transthoracic puncture was performed in the subxyphoid area under fluoroscopy guidance. A 7 Fr quadripolar catheter was inserted in the epicardial space through an 8 Fr sheath for mapping and ablation. An endocardial catheter was positioned in the middle cardiac vein (MCV) for simultaneous endocardial-epicardial mapping. A ventricular electrogram (20 msec) and AP potential (30 msec) earlier than the delta wave were recorded in the epicardial space. During the first RF energy delivered in the epicardial space to the distal ablation catheter resulted in loss of preexcitation in the third brat. After 45 minutes, coronary artery angiography was repeated which showed no injuries. No complication was observed in the procedure. After 8 months of follow-up the patient presented no further supraventricular tachycardia and no recurrence of preexcitation.
Conclusion: Epicardial ablation of accessory pathways is feasible and may be a useful alternative for AP with epicardial course not achievable via MCV.

P1559 The risk factors of atrial fibrillation in patients with Wolff-Parkinson-White syndrome

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AF is observed more often in patients (pts) with WPW than in the general population. The aim of this research was to compare the differences between risk factors of AF in pts with WPW and AF vs pts without AF.
Group and method: We analyzed 239 pts with WPW. Gr.1-81 pts with AF (23F, age 43±15), gr.2-158 pts without AF (91F, age 34±15) We analyzed risk factors such as: sex, age, syncope, atrioventricular tachycardia (AVT) rate, other arrhythmia, CHD, HT, small and moderate mitral valve insufficiency (IM), other diseases, echocardiography findings, number of accessory pathways (AP) and its localization, effective refractory periods (ERP) of the atrium, ventricle, atrioventricular node and AP.
Results: In multifactoral analysis only sex, age and syncope were AF risk factors. In logistic regresion age, sex, syncope, CHD, HT and IM increased AF occurrence. Also in AF patients VF and AFl occurred more often and concealed AP occurred seldom. In patients with WPW and AF there was a trend of more left free wall (LFW) and right postero-septal (RPS) AP location. We did not observe significant differences in AVT rate, other diseases, echocardiography findings and refractory periods.

	Sex	Age	Syncope	VF	CHD	HT	IM	LFW	AP retro	Multiple AP	AVT rate
AF-81 pts	23F	34±15	35	11	13	21	40	67	9	19	210
No AF-158 pts	91F	43±15	36	3	12	24	46	102	51	26	217
P	0,0001	0,001	0,001	0,002	0,04	0,04	0,01	0,04	0,002	NS	NS

AP-accessory pathway, AVT rate-maximal rate of atrio-ventricular tachycardia, CHD-coronary heart disease, F-female, HT-hypertension, IM - small or moderate mitral valve insufficiency, LFW-left free wall AP localisation, pts-patients, retro-retrograde conduction only

Conclusions: 1. In pts with WPW age, sex (more AF in men), and syncope are independent risk factors of AF.
2. There was significantly more VF in pts with WPW and AF than in the group without AF.

SYNCOPE

P1560 Prevalence and triggers of syncope in young adults: a questionnaire

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Background: To learn more about the true prevalence of syncope in a young healthy population we performed a descriptive study among the medical students in the Academic Medical Centre. Our first study objective was to determine the prevalence of syncope in a young population, including the recurrence rate. Other study objectives included the evaluation of the gender difference in syncope and the evaluation of the triggers provoking syncope in young adults. The main part of the questionnaire we developed consisted of questions about the history of syncope, the frequency of syncope and triggers of syncope.
Results: The questionnaire was handed out to 395 students. Seventeen students did not fill in their gender. The remaining group consisted of 254 (64%) women and 124 (31%) men. The gender distribution is in accordance with the overall ratio of female and male students in our curriculum. The median age for female and male students was 21 years.
Of all 395 students 154 (39%;95%CI 34-44) reported that they had experienced at least one (episode of) syncope. The prevalence of syncope was almost twice as high in women compared to men (47% vs. 24%; RR 1.9, 95%CI 1,4-2,7). The mean age at which the first syncope occurred was not significantly different between women and men (14.3 and 14.8 years respectively). Female as well as male students mentioned a diverse range of triggers. Being in a warm environment and prolonged standing was mentioned by respectively 47 (12%) and 41 (10%) students. Other frequently named triggers were pain, illness, alcohol and drugs, emotion, seeing blood, standing up, insufficient food intake and tiredness. Many students marked a combination of triggers as the cause of an episode of syncope.
Conclusions: Syncope is common in young adults. The majority of triggers involved in syncope in young adults are mostly common daily activities and circumstances.

P1561 Efficacy of correction of subclavian stenosis/occlusion in patients with subclavian steal and previous by pass internal mammary-IVA

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Background: Steal syndrome and subclavian steal syndrome are a complication of atherosclerotic disease.Such syndrome have numerous anatomic and clinical variations whose common haemodynamic characteristic is the presence of haematic vertebral-subclavian.In such conditions, a considerable amount of blood is diverted from the cerebral area to re-occupy the upper limb,and the quantity of blood used depends on both the stenosis level of the subclavian artery in prevertebral area and the activity of upper limb.In the last few years,episodes of subclavian steal had left internal mammary artery-interventricular anterior artery (LIMA-IVA)bypass graft.The aim of this report is the evaluate the efficacy of subclavian steno-occlusion corrective treatment in surgical patients with a vertebral-subclavian haematic steal syndrome.
Methods: We observed 207 patients aged between 48 and 77 years who had the LIMA-IVA bypass graft,through ecocolordoppler.Of these,31 patients turned out to be affected by steno-occlusion of the homolateral subclavian artery.10 patients(group 1)had less than 30% of subclavian stenosis and showed latent vertebral-subclavian steals;they were treated with acetylsalicylic acid and ticlopidine. 7 patients (group 2) had 50% to 70% subclavian stenosis and presented an intermittent vertebral-subclavian steal;only 4 of these patients were treated with angioplasty and stent application to the subclavian artery and 3 were treated with acetylsalicylic acid and ticlopidine.14 patients(group 3)had more than 70% stenosis(11 patients)or total occlusion(3 patients)of the subclavian artery and were treated with angioplasty and stent application or carotid-subclavian bypass graft.All the patients were checked every three months for a period of 5 years after the diagnosis.
Results: Ther first group of patients showed no angina and no sign of subclavian restenosis.In the second group only two patients, affected by angina,showed subclavian restenosis at angiography and were again treated with angioplasty and stent.In the third group only one patient underwent further angioplasty with stent for restenosis.
Conclusion: The results of this study showed that the subclavian steal syndrome may be adverse event in patients subjected to LIMA-IVA bypass graft.The identification of the haematic kind of steal is essential in an appropriate therapeutic approach.The study also indicated that steal syndrome can cause the development of more serious symptoms which cannot be medically treated.

P1562 Diagnostic yield of supine and upright carotid sinus massage in patients with unexplained syncope

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Carotid sinus hypersensitivity (CSH) as a cause of syncope (Sy) is frequently underdiagnosed, and its prevalence in patients (pts) with unexplained syncope (un-Sy) is unknown. The aim of the present study is to establish prospectively the diagnostic value of supine and upright carotid sinus massage (CSM) in pts with un-Sy referred to a syncope clinic.

Method: 317 patients (age: 53±20 y, female 46%) with 6 un-Sy on average (range 1-200) have been consecutively included in a targeted work-up (WU). Our WU started with a 20 min detailed interview, followed by a head-up tilt test, and an upright and supine CSM. A CSM was considered positive when both following criteria were met: 1) a pause ^{3}3 s (cardioinhibitory form, CI), a drop in systolic blood pressure (SBP) ^{3}50mmHg (vasodepressive form, VD), or both together (mixed form), and 2) if the positive CSM appeared reasonably as the cause for the spontaneous episodes of un-Sy.

Results: A CSM was performed in 89% (283/317)of the pts, and was considered diagnostic in 35% (99/283). The following CSH forms were observed: VD in 61%, CI in 17% and mixed in 22%. 77% (76/99) of the pts with a positive CSM were tested in both positions: the supine position alone was positive in 5%, the upright position alone in 61%, while both positions together were positive in 34% of the pts. 51% (39/76) of the positive CSM tested in both positions reported symptoms, during the upright position in 75% or in both positions in25%, but never during supine CSM. Among the 39 symptomatic pts, a vertigo was reported in 50%, a dizziness/pre-syncope in 48%, and a syncope in 20%. One transient neurological complication (hemiparesia) was reported in the 601 CSM (prevalence 0.17%) performed or in the 283 pts (prevalence 0.35%) tested. In the 99 pts with a diagnostic CSM, the decline in SBP was significantly higher (42 vs 29 mmHg, $p<0.01$) and the increase in the RR interval significantly smaller (1185 vs 1610ms, $p<0.01$) in the upright as compared to the supine position. No difference was observed between the symptomatic and asymptomatic pts with a diagnostic CSM.

Conclusion: In pts with un-Sy, the prevalence of CSH after a negative WU is as high as 35%, with nearly 2/3 of VD form. Because symptoms were only reported in the upright position, a negative supine CSM should be followed by a supine test, especially if one considers to use the so-called "method of symptoms". Because of the low prevalence of complications, CSM can be safely performed in both positions.

P1563 Recurrency of neurocardiogenic syncope is independent of treatment

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Clinical predictors of recurrence in patients with neurocardiogenic syncope are poorly defined and at the present time there is no optimal treatment that could favorably influence the natural course of this common and threatening condition. We have completed a retrospective analysis of the 417 subjects with unexplained syncope that underwent a tilt table test (TT) from March 1994 till June 2001. The mean follow-up period from the TT to the last interview was 47 ± 25 months and the mean age of the population under study was 38 ± 20 years, with a sligthly more frequent incidence of women (214, 51.3%) over men (203, 48.7%). The TT was considered positive in 136 patients (32.6%), negative in 279 patients (66. 9%) and indeterminate in 2 patients (0.5%). Of the 136 positive TT, 19 (13.97%) showed a cardioinhibitor response, 56 (41.17%) a vasodepressor response and 61 (44.85%) a mixed response. During the the follow-up 275 (65.9%) patients had no recurrent events while 125 (29.9%) patients showed one or more fainting episodes and 17 (4.07%) patients were lost to followup. The incidence of recurrent events was 0.9 ± 2.03 per patient - year. Recurrence of syncope could not be predicted from the type of positive TT response; it was recorded in 7 of the 19 patients with an inhibitory response (58.33%), 11 of the 56 patients with a vasodepressor response (19.6%) and 22 of 61 patients with a mixed response (36.06%), P= 0.095. Recurrent syncope was more frequent in patients with a mixed than in patients with a vasodepressor response (P= 0.04), but there was no significant difference when we compare the patients with the mixed response and the patients with the cardioinhibitory response (P= 1.00), or this latter group and the patients with the vasodepressor response (P=0.21). The records of 402 patients (96%) were available for post-TT treatment analysis and we found that treatment had no influence on recurrence of syncope. Thus, recurrent events were as frequent in the 265 (65.9%) patients that received no treatment as in the 137 (34.07%) patients that received treatment as a result of a positive TT (P= 0.06).

Conclusions: The TT seems to have a therapeutic effect itself. Our findings suggest that the type of TT has no predictive power for the recurrence of neurocardiogenic syncope. However, patients showing a mixed response on the TT are more prone to suffer recurrent neurocardiogenic syncope. Finally, no treatment seems to offer any significant protection against recurrent neurocardiogenic syncope.

P1564 Supraventricular tachycardias are a frequent cause of dizziness and syncope

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Dizziness/syncope is a frequent event in population without heart disease and their causes remain difficult to elucidate. The objectives of the study were to determine the diagnosis value of esophageal electrophysiological study for the evaluation of sino-atrial and AV nodal conduction, for the induction of supraventricular tachycardia and for the assessment of the mechanism of dizziness/syncope in patients with normal ECG and without heart disease.

Population and methods: 145 patients aged from 20 to 87 years, without heart disease, with a normal ECG in sinus rhythm complained of dizziness and syncope; 56 patients had also a feeling of palpitations or tachycardia associated with syncope; the patients had no significant arrhythmia on the 24 hour Holter monitoring. Electrophysiologic study was performed during a consultation by transesophageal route: rate of occurrence of 2nd degree AV block during atrial pacing and sinus node recovery time were measured; programmed atrial stimulation using 1, 2 atrial extrastimuli were performed in basal state and after infusion of 20-50 μg of isoproterenol; arterial blood pressure was monitored.

Results: 1) study was negative in 43 patients (30%); 2) sinus node dysfunction was noted in 10 patients (7%); 3) vasovagal reaction reproducing spontaneous symptoms was provoked by isoproterenol infusion in 15 patients (10%); 4) sustained atrial fibrillation was induced in 22 patients (15%); 5) paroxysmal junctional tachycardia was induced in 55 patients (38%). Patients with negative study were more frequently females (64%)than males (36%) and were younger than those with sinus node dysfonction or atrial fibrillation (respectively 44±21 years and 71±9, 63±14). Patients with vasovagal reaction were more frequently males (59%) than females (33%)and were significantly younger than all the other subgroups (36±21 years). The treatment was guided by these data: advices, pace-maker,beta-blockers, antiarrhythmic drugs or radiofrequency ablation of reentrant circuit were indicated according to the diagnosis and suppressed syncope in all patients but 2.

Conclusion: esophageal electrophysiologic study performed during a consultation was a safe, rapid and economic means to detect an arrhythmia in 60% of patients complaining syncope, especially those with palpitations. Supraventricular tachycardia clearly was an underestimated cause of dizziness and syncope.

P1565 Comparison between the postural blood pressure test and the head-up tilt test in patients with recurrent syncope of unexplained origin

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The postural blood pressure test identifies patients with an orthostatic hypotension and the head-up tilt test is used to detect the neurocardiogenic reflex-mediated origin of syncope. The aim of the investigation was to compare the two tests in patients with recurrent syncope of unexplained origin.

Methods: The study included 48 out-clinic patients who were referred for a head-up tilt test. All patients underwent a postural blood pressure test and separately a head-up tilt test. For the postural blood pressure test the patients stood up for 5 minutes. A positive postural blood pressure test was defined by more than 10 mmHg decrease of systolic blood pressure, by more than 5 mmHg decrease of diastolic blood pressure or by a drop of more than 5 bpm of the heart rate. The head-up tilt test consisted of a drug-free stage with a 60-degree angle of tilt for 45 minutes and a provocation stage with nitroglycerin.

Results: There were 25 patients with a positive (54 ± 17 years, male n = 11; 44%) and 23 patients (65 ± 4 years, male n = 13; 65%) with a negative postural blood pressure test. The demographic data of the two groups were not significantly different. Patients with a positive test had a history of 22 ± 69 syncope and patients with a negative test of 11 ± 13 syncope (negative) syncope (not significant (ns). The patients had during the last 6 months 3.7 ± 5.7 (positive) and 2.1 ± 3.9 (negative) syncope (ns). A positive head-up tilt test had 13 (52%) patients with a positive and 11 (48%) with a negative postural blood pressure test (ns). The head-up tilt test became positive during the drug-free state in 6 (positive) and 8 (negative) and during the provocation stage in the 7 (positive) and 3 (negative) pts (ns). The time until the head-up tilt test became positive was 18 ± 22 min (positive) and 12 ± 18 min (negative), respectively (ns). During 28 ± 10 months follow-up recurrent syncope had 8 (32%) patients with a positive and 7 (30%) patients with a negative test (ns).

Conclusions: The postural blood pressure test had in patients with recurrent syncope of unexplained origin no predictive value for a positive head-up tilt test. The findings indicate that there is no close association between orthostatic hypotension and vasovagal syncope.

P1566 Results of shortened head-up tilt testing potenciated with sublingual nitroglycerin in a large cohort of patients with unexplained syncope

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Background: In spite of its clinical acceptance as a test to diagnose vasovagal syncope, head-up tilt test (HUT) continues to be limited in use partly because of the lack of a standardized test protocol and the lengthy duration of a complete study. Recently, a new simplified and time-saving protocol, including the sublingual administration of nitrogyicerin (NG) ("the Italian Protocol"), has been proposed as standard method of HUT. In the present study we evaluated the diagnostic value of HUT potenciated with NG on a large cohort of patients with recurrent syncope of unknown origin.
Methods: 426 patients (230 men and 196 woman, mean age 44.6 ± 19.4 years) with recurrent syncope (mean 5.4 ± 7.2 events), no structural heart disease and normal baseline ECG were studied. We also studied 15 healthy volunteers 8 men and 7 women, mean age of 43 ± 20 years. HUT was performed at 60° for 20 minutes; if negative, 400 ìg sublingual NG spray was given and the test continued for a further 15 minutes. Blood pressure and cardiac rhythm were continuously monitored.
Results: Sixty-one (14.3%) patients had a positive response during the initial unmedicated phase; 365 (85.7%) had no symptoms and underwent NG test. The mean time to syncope was 10.5 ± 5.7 min. After administration of sublingual NG spray, another 194 patients (53.2%) had a positive HUT. The mean tilt time for the NG positive patients was 4.7 ± 2.1 min. An exaggerated response was ilicited in 27 patients (7.4%). Patients with positive baseline HUT were younger (35.5 ± 19.4 vs 46.5 ± 19.3; $p < 0.001$) and suffered more syncopal events (10.5 ± 5.7 vs 4.7 ± 2.1; $p < 0.001$) that those with positive NG HUT. No control subject had a positive reponse during the unmedicated phase. Two (13.3%) subjects (mean age 43 ± 18 years, 1 man and 1 woman) had a positive reponse to the NG test, 11 (73.3%) a negative response and 2 (13.3%) an exaggerated response (mean age 46 ± 19 years, 1 man and 1 woman). The total positivity rate was 60% with a specificity rate of 85.7%.
Conclusions: In patients with syncope of unknown origin, shortened HUT potentiated with sublingual NG was found to be fairly sensitive and highly specific in inducing vasovagal responses.

P1567 Situational syncope: prevalence, response to head-up tilt testing and follow-up

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The prevalence of situational syncope (SS) among patients (pts) with neurally-mediated syncope (NMS) is not fully investigated. Additionally, the rate of positive response to head-up tilt testing (HUT) in pts with SS and their follow-up (FU) have not been studied in detail. The aim of this study is to further elucidate these issues.
Methods: We prospectively studied 121 pts (mean age 42±17 yrs, 51 men and 70 women) with history of recurrent NMS. They had normal electrophysiological study and they were free of structural heart disease. Before study inclusion, they underwent a HUT (60° tilting for 30 min and if negative, isoproterenol infusion) and then, they were followed-up for 6 months. Pts with VVS were treated with propranolol, while pts with SS were advised to avoid the trigger event. The prevalence of SS among the study population was assessed. For each pt we compared the number of syncopal spells (sync) during the last 6 months before study inclusion with that during FU.
Results: In a total of 121 pts with NMS, 28% had SS. Their syncopal attacks were associated with meal (15 pts, 44%), micturition (14 pts, 41%), defecation (3 pts, 9%), cough (1 pt, 3%) and swallowing (1 pt, 3%). The remaining pts (72%) had VVS. The response to HUT and the number of sync before and during FU were similar in pts with SS and VVS (p:NS). Ten out of the 34 pts with SS (29%) had also experienced occasional episodes of VVS. They had similar response to HUT and prognosis to those without VVS attacks (p: NS).

	number of pts	positive HUT	sync last 6 months	sync during FU
VVS	87 (72%)	37 (43%)	2.2±0.4	0.2±0.3
SS	34 (28%)	16 (47%)	2.1±0.4	0.1±0.3

(mean values ± SD).

Conclusions: In our study, pts with SS constituted a considerable proportion of pts with NMS. Although SS and VVS may differ in the mechanism of sync, they had similar response to HUT and similarly benign prognosis. Furthermore, the coexistence of occasional VVS episodes in pts with SS was not associated with a higher rate of positive response to HUT or worse natural history.

P1568 Clomipramine infusion during tilt to imply the neurocardiogenic origin of syncopes and presyncopes of unknown etiology

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Clomipramine (CP) was recently proposed as a new drug challenge during tilt test (T) for the diagnosis of neurocardiogenic syncope (NCS). The aim of this study was to prospectively evaluate the diagnostic accuracy for NCS of two T strategies in 477 consecutive patients (pts) [mean age (m.a): 47.8 ± 23.5 years; male: 288 (60.4%)] with syncopes (S)/presyncopes (PS) of unknown etiology after negative clinical and non invasive investigations.
Methods: Group A: the first 319 patients (pts) [192 (60.2%) male; m.a = 49.7 ± 23 years] were tilted at 60° for 30 minutes (min), then for 15 min with 2 μg/min isoproterenol infusion rate. Group B: the following 158 pts [95 (60.1%) male; m.a = 43.1 ± 24.6 years] were tilted at 60° for 20 min with 5 mg CP infused during the first 5 min of T. S/PS with bradycardia/asystole and concomitant fall in blood pressure were considered as positive (+) response for NCS.
Results: There was no significant difference between group A/B in age, sex-ratio, S [239 (74.9%) versus (vs) 112 (70.9%) pts], mean number of events per pt (5.7 ± 10.3 vs 3.7 ± 6.2), concomitant drugs [116 (36.4%) vs 69 (43.8%) pts], past history [diabetes = 9 (2.8%) vs 4 (2.5%) pts; hypertension = 62 (19.4%) vs 25 (15.8%) pts].T was positive in 99 (31.1%) pts for A group and 101 (63.9%) for B group. T (+) ratio was identical in pts < 35 years [A group = 40/119 (33.6%); B group = 41/60 (68.3%)].
Conclusion: CP during T increases significantly the accuracy of the test for NCS diagnosis. If previously reported specificity (87 to 94%) was confirmed, CP-T might be the most valuable tool in the evaluation of pts with S or PS of unknown etiology.

P1569 The first recurrence of syncope within 1 month after a positive head-up tilt table test result predicts syncopal freq. in the long-term follow-up

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Background: There are some clinical observations that vasovagal syncope shows predictable variations in frequency, often in the form of "clustering of events". However there were some indications that timing of the first syncope after positive head-up tilt table test (HUT) could predict the frequency of the events thereafter.
Objectives: The aim of this study was to determine whether the first recurrence of syncope within 1 month after positive HUT result, in the patients tested for suspected vaosovagal or syncope of unknown aetiology, predicts the incidence of syncope during long- term follow-up.
Methods: Eighty patients (43M, 37F, median age 48 years) with syncope, and positive basal tilt-table test according to Westminster protocol, or combined-"hybrid" test with isoproterenol/NTG, were included in this study. Patients with at least one syncope spell after a positive HUT were followed up for up to 8 years (mean 50 ± 18 months). The time from tilt table testing to the first recurrence of syncope was correlated.
Results: Patients who had the first syncope within 1 month of tilt testing, had significantly more spells during follow up (median 14 > 4 spells, t-4.0 $p < 0.00015$). Compared with patients who fainted for the first time one month after testing, the syncope rate or spell frequency was significantly higher as well (0.70 spells/month vs. 0.20 spells/month).
Conclusions: The time to the first recurrent syncope predicts the frequency of sycopal attacks after a positive tilt table test result.The patients with fisrt reccurence within one month have significantly higher rate of episodes thereafter in longterm follow-up period. This could have important role in managing patients with vasovagal syncope, especially according timing and mode of treatment.

ATRIAL FIBRILLATION – ELECTRICAL CARDIOVERSION

P1570 Thromboembolic complications after cardioversion of atrial flutter in comparison to atrial fibrillation

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Aim of the prospective single center observational study was to evaluate the thromboembolic risk after electrical cardioversion in 386 patients (pts) with atrial flutter (73% male, mean age 63 ± 12 years, organic heart disease 48%, atrial hypertension 43%, diabetes mellitus 14%, left atrial diameter 41 ± 8 mm, history of stroke 4%) compared with the thromboembolic risk in 1269 pts with atrial fibrillation (74% male, mean age 63 ± 10 years, organic heart disease 57%, atrial hypertension 54%, diabetes mellitus 12%, left atrial diameter 46 ± 6 mm, history of stroke 10%).
Methods: Anticoagulation strategy was similar in pts with atrial flutter and atrial fibrillation (effective anticoagulation at least 3 weeks before and 8 weeks after electrical cardioversion). Transesophageal echocardiography (TEE) was performed in 144 pts with atrial flutter and in 845 pts with atrial fibrillation before cardioversion.
Results: Pts with atrial fibrillation had more often an organic heart disease (57% vs 48%, p = 0.01) and more often a history of stroke (10% vs 4%, p = 0.001) compared to pts with atrial flutter. TEE revealed left atrial thrombi in 7.7% of pts with atrial fibrillation, in contrast to 4% in pts with atrial flutter.

	Atrial Fibrillation (1269 pts)	Atrial flutter (386 pts)
Cardioversion performed	1091 pts (86%)	341 pts (88%)
Embolic events < 48 h	2 pts (0.16%)	2 pts (0.52%)
Embolic events > 48 h < 4 weeks	9 pts (0.7%)	1 pt (0.26%)
Overall embolic events	11 pts (0.86%)	3 pts (0.78%)

Conclusion: Pts with atrial fibrillation had twice as much a history of stroke than pts with atrial flutter. Left atrial thrombi were detected twice as often in pts with atrial fibrillation than in pts with atrial flutter (7.7% vs. 4%). The embolic risk during the first 4 weeks after electrical cardioversion was similar in pts with atrial flutter and atrial fibrillation (0.78% vs. 0.86%).

P1571 Is direct current cardioversion in patients with atrial fibrillation safe? Complication rate in 1269 consecutive patients

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Background: Direct current cardioversion (CV) of atrial fibrillation (AV) is the most effective method to restore normal sinus rhythm; however little is known about the complication rate of CV, if the recommended guidelines for anticoagulation prior to CV were followed.
Aim of this prospective study was to assess the complication rate of CV in patients (pts) with persistent AF.
Methods and Results: The study group comprised 1269 consecutive unselected pts with persistent AF who were admitted for CV of AF. In 845 of 1269 pts (67%) a transesophageal echocardiography (TEE) was performed before CV. At the time of intended CV anticoagulation was effective (INR 2-3) in 85% of pts. In 984 of 1269 pts (78%) CV was performed. All complications associated with CV, which occurred in between 48 h were registered. The complications associated with CV are listed below. None of the complications were associated with the TEE. Overall acute success rate of CV was 84%.

Complication of 1269 external CV

	Number of patients	in %
Asystole	3 pts	0.3
AV-block III	1 pt	0.1
AV-block II	3 pts	0.3
Sinus bradycardia	2 pts	0.2
Ventricular fibrillation	1 pt	0.1
Pacemaker malfunction	1 pt	0.1
Transient ischemic attack	2 pts	0.2
Adverse effect of etmoidate	2 pts	0.2
Overall complications	15 pts	1.5

Conclusion: Complication rate after CV is low with 1.5%. Arrhythmogenic complications were the most common complications after CV (1.1%). In 2 pts (0.2%) a transient ischemic attack occurred in between 48 h after CV despite effective anticoagulation and normal TEE.

P1572 Efficacy of monophasic and biphasic shocks for transthoracic cardioversion of chronic atrial fibrillation and post-shock skeletal muscle injury

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Efficacy of monophasic and biphasic shocks for transthoracic cardioversion of chronic atrial fibrillation and post-shock skeletal muscle injury
Background: Biphasic (B) compared to monophasic (M) shocks are supposed to be more efficient for transthoracic cardioversion of chronic atrial fibrillation (AF); requiring less current and causing less post-procedure pain. We hypothesized that B shocks would have higher success rate and cause less skeletal muscle injury.
Methods: Eighty patients with chronic AF were randomised to receive either truncated exponential B (70, 100, 150 and 200 J) or damped sine wave M (100, 200, 300 and 360 J) sequential impedance compensated shocks. Crossover shock of maximal energy of the other waveform was delivered if AF persisted. Plasma levels of cardiospecific troponin T (cTnT), creatine kinase (CK) and myoglobin before, 6 hours and 24 hours after procedure were determined.
Results: Cumulative success rates were not significantly different between B and M shocks (37/41 (90.2%) vs. 36/39 (92.3%), respectively). Compared with M shocks, B shocks succeeded with less peak-current (17.5 ± 4.4 vs. 36.0 ± 8.0 A, p <0.0001), less cumulative energy (243 ± 164 vs. 507 ± 298 J, p < 0.0001) and less cumulative current (33.7 ± 19.0 [9-84] vs. 72,0 ± 30.9 [22-141] A, p < 0.0001). All crossover shocks failed. In all patients cTnT remained under discriminatory level (0.1 μg/l) of myocardial injury. Compared to M shocks, B shocks resulted in lower maximum level of CK (1.55 ± 3.91 vs. 8.50 ± 11.83 μkat/l, p < 0.001) and lower maximum level of myoglobin (87.04 ± 114.52 vs. 445.52 ± 525.93 ng/ml, p < 0.0001). The M shocks (relative risk 5.37, 95% CI 2.53-11.4, p<0.025) and cumulative current (relative risk 5.49, 95% CI 2.39-12.60, p<0.04) were independently associated with high myoglobin concentrations.
Conclusions: M and B shocks are similarly efficient for transthoracic cardioversion of chronic AF, and do not cause any myocardial damage. M shocks, and cumulative current are independently associated with skeletal muscle injury.

P1573 Highly successful atrial defibrillation using low-energy biphasic waveforms with no tilt

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Background: Conventional capacitor discharge defibrillators deliver shock waveforms with considerable tilt. The efficacy of defibrillation may be improved by reducing the tilt of the waveform. We investigated the feasibility, efficacy and safety of a novel device that delivered a biphasic direct current shock without tilt (square waves) in transvenous cardioversion of atrial fibrillation (AF).
Methods: The device was assessed in 10 anaesthetised and ventilated pigs (58 ± 2kg). Defibrillation leads were positioned fluoroscopically, one in the distal coronary sinus and the other in the lateral right atrium via the external jugular vein. The leads were then connected to the output of the novel defibrillator. Sustained AF was induced by rapid atrial pacing (Grass stimulator, 100Hz, 5 Volts). The biphasic waveform was assessed at two pulse width (PW) settings of 3/3 ms and 6/6 ms, and at varying first and second phase voltage settings ranging from 25 V to 100 V. Five attempts at cardioversion were made at each pulse width and voltage setting. Success was defined as reversion to sinus rhythm within 5 beats of shock delivery.
Results: No arrhythmic complications were observed for the total 750 shocks delivered (including 50 placebo shocks delivered to a 50 Ohm dummy load during AF). Data are expressed as mean % success (mean energy, J). PW 6/6ms: 50/-25V=92(0.35J), 75/-37.5V=98(0.82J), 100/-50V=100(1.45J), 25/-25V=24(0.12J), 50/-50V=80(0.54J), 75/-75V=98(1.27J), 100/-100V=100(2.26J); PW 3/3ms: 50/-25V=58(0.21J), 75/-37.5V=84(0.49J), 100/-50V=96(0.87J), 25/-25V=20(0.07J), 50/-50V=74(0.31J), 75/-75V=98(0.72J), 100/-100V=100(1.29J);Placebo: 6/6ms, 100/-50V to dummy load =6(0.00J).The 6/6ms 50/-25V setting was more efficacious than the 3/3ms 50/-50V (p= 0.002) and the 6/6ms 50/-50V settings (p=0.083).
Conclusion: Cardioversion using this novel biphasic waveform is safe and efficacious at very low voltage. The 6/6ms PW setting is more efficacious than the 3/3ms PW setting. The voltage setting at 50% second phase voltage was more efficacious than the setting with equal first and second phases. Design modification will enable the device to be used as an implantable defibrillator.

P1574 Electrical cardioversion of long lasting atrial fibrillation: analysis of success and recurrences

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The success rate of electrical cardioversion (CV) of atrial fibrillation (AF) seems to be inversely related to the duration of this arrhythmia. Thus, in clinical practice many patients (pts.) with AF lasting longer than one year are not considered to be candidates for a CV.

Purpose: Our aim was to evaluate success and recurrence rates in pts. with long lasting AF.

Method: 345 consecutive pts. with AF were enrolled in the Urban-AF-Database between Oct. 1998 and Dec. 1999(males 57%, mean age 66±11 years). Persistent AF was observed in 58% of pts. (201/345). AF lasted <= 1 year in 43% (86/201) (Group A). AF > 1 year was found in 57% (115/201)(Group B). Electrical cardioversion was attempted in all eligible cases regardless the duration of AF. A follow up at 12 month was achieved in 85% (171/201) of cases.

Results: No significant difference between both groups was observed with regard to age (66 vs. 67 years), gender (69 vs. 60% males), hypertension (59 vs. 52%), coronary artery disease (34 vs. 34%), valvular heart disease (6 vs. 9%), dilative cardiomyopathy (11 vs. 14%) and lone AF (9 vs. 14%). Electrical CV was attempted in 55% (group A) and 40% (group B) of pts. In group A 87% and in group B 71% of pts. were discharged in sinus rhythm (SR) after successful electrical CV. At a follow-up of 12 months 46% (group A) and 30% (group B) of pts. remained in SR (p = 0.16, ns).

Conclusion: 1. These data demonstrate that about 70% of pts. with long lasting AF can be discharged in SR. 2. There was no significant difference with respect to recurrence rate between patients with AF lasting longer or less than 1 year. Therefore, in clinical routine even in pts. with long lasting AF restoration of SR should be attempted.

P1575 Clinical value of left atrial appendage velocities for predicting of cardioversion success of atrial fibrillation of unknown duration

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Background: Duration of atrial fibrillation (AF), left atrial appendage (LAA) flow velocity pattern determined by transesophageal echocardiography and left atrial diameter provide valuable information for prediction of outcome of electric cardioversion (ECV) in patients with non-valvular AF. However, in substantial number of patients the duration of AF is unknown.

Objective: To evaluate the predictive power of LAA anterograde flow velocity for prediction of outcome of ECV in patients with AF of unknown duration, in a prospective, multicenter, international study design.

Methods: One hundred-ninety one consecutive patients (130 males, mean age 66±11 years) with non-valvular AF of unknown duration underwent transthoracic and transesophageal echocardiography < 24 h before ECV.

Results: ECV was successful in restoring sinus rhythm in 135 patients (71%). Neither the clinical (sex, body mass index and underlying diseases) nor the transthoracic echo parameters (left atrial diameter; left ventricular mass, end-diastolic diameter and ejection fraction) predicted the success of ECV, only the age tended to be lower (63.9±12.5 vs 67.2±10.3 years, p=0.061) in patients with successful ECV. On the basis of transesophageal echocardiographic variables, successfully converted patients had a significantly higher mean LAA emptying flow velocity than those with failure of ECV (29.1±14.6 vs 24.1±13.3 cm/sec; p=0.029), whereas the presence or absence of left atrial spontaneous echo contrast or the degree of mitral regurgitation provided no additional information.

Conclusion: In patients with non-valvular AF of unknown duration, measurement of LAA flow profile before electrical cardioversion provides valuable information for prediction of cardioversion success.

P1576 Clinical predictors of successful cardioversion of persistent atrial fibrillation with a balloon-tipped internal cardioversion catheter

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Background: Cardioversion of atrial fibrillation (AF) is feasible by either pharmacologic or electric approaches. Both treatment modalities carry a high risk of relapse to AF within one month. The variables associated with successful cardioversion and recurrences of AF after pharmacologic or external direct current cardioversion have been extensively studied; yet those predictive of success rate after internal cardioversion (ICV) and relapse to AF are not well characterized.

Methods and Results: We studied 109 patients with persistent AF (63±9 years, 57% male, mean duration: 23±34 months) treated with ICV using a balloon-tipped pulmonary artery catheter (ALERT®, EP MedSystems, Inc) with distal and proximal shock electrodes and biphasic shocks. One hundred of 109 patients (92%) were defibrillated successfully. Stepwise logistic regression analysis revealed that, left ventricular ejection fraction followed by left atrial diameter were the most significant independent predictors for conversion to sinus rhythm (p=0.011 and p=0.043 respectively). The mean energy for successful cardioversion was 7.8±3.2J. At one month of follow up AF recurred in 45 patients (45%). No clinical variable was found to predict recurrence within this interval. The table shows association between the test variables and success of ICV.

	Success	Failure	p
Age (yrs)	63±9	64±7	ns
Gender: m/f	57/43	5/4	ns
AF duration (months)	23±35	16±19	ns
LVEF (%)	51±11	59±7	0.011
LA diameter (mm)	44±4	48±3	0.043

Conclusions: Internal cardioversion is a very effective method for the restoration of sinus rhythm in patients with persistent atrial fibrillation. Success rate is associated with lower ejection fraction and smaller left atrial diameter, independent of AF duration. These findings may be useful for the most appropriate selection of patients for internal cardioversion.

P1577 Internal cardioversion as an alternative option to external cardioversion of atrial fibrillation in patients with congestive heart failure

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Background: Atrial fibrillation (AF) is very common among patients with congestive heart failure (CHF). External cardioversion is often unsuccessful in these patients. Although internal cardioversion (ICV) has been frequently used in patients refractory to external cardioversion, this has been rarely performed in CHF patients, also due to the described high incidence of early recurrences. Aim of the study was to estimate the incidence and to evaluate potential predictors of early recurrences among patients with CHF and persistent AF.

Methods: Twenty-nine pts with CHF, persistent AF (3 months-5 years) and previous failed external CV, underwent ICV. Mean age was 65±7 years, mean NYHA class 2.7±0.6; all pts had a dilated left ventricle (LVEDD) with mean ejection fraction (LVEF) 31±7% and left atrial diameter (LAd) 52±7 mm. All patients received amiodarone 400 mg daily 4 weeks before and 200 mg daily after ICV.

Results: No significant adverse effects were observed during the procedure. Sinus rhythm (SR) was restored in twenty-six patients (86%) with a mean energy of 12±4 J. In three patients AF recurred within few minutes, in three within 24 hours, in six additional patients within one month. Comparison of patients in SR (14/29, 48%) vs. patients in AF at 1 month shows that patients with AF recurrence had significantly higher duration of arrhythmia (see table).

	Age (yrs)	NYHA	AF (months)	LVEF (%)	LVEDD (mm)	LAd (mm)
1 month SR	67 (8)	2.8 (0.5)	21 (28)	34 (7)	62 (12)	51 (6)
1 month AF	64 (6)	2.7 (0.5)	44 (22)	30 (7)	60 (14)	55 (9)
p value	0.4	0.6	0.048	0.6	0.8	0.3

Data of the two groups are presented as mean(SD)

Conclusions: Internal cardioversion, associated with amiodarone pretreatment, is safe and can effectively restore sinus rhythm, preventing recurrences in many patients with congestive heart failure and persistent atrial fibrillation.

P1578 Clinical value of left atrial appendage flow velocity for predicting of cardioversion success in patients with persistent atrial fibrillation

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Background: Echocardiographic parameters for predicting cardioversion outcome in patients with persistent non valvular atrial fibrillation are not accurately defined.
Aim: To evaluate the role of left atrial appendage flow velocity detected by transesophageal echocardiography for prediction of cardioversion outcome in patients with persistent non valvular atrial fibrillation.
Methods: 62 patients (38 males, mean age 68±11 years) with persistent non-valvular atrial fibrillation of duration of more than 4 weeks but less 12 months duration underwent transthoracic and transesophageal echocardiography before electrical cardioversion.
Results: Cardioversion was successful in restorig sinus rhythm in 54 patients (87%). Mean left atrial appendage peak emptying flow velocity was significantly higher in patients with successful than those with unsuccessful cardioversion (34±16.4 cm/sec vs 24.3±14.7 cm/sec; $p < 0.001$); other independent predictors of cardioversion success at univariate analysis were left end-diastolic diameter > 57 mm ($p < 0.05$), ejection fraction > 50% ($p < 0.04$) and the pretreatment with antiarrhythmic drugs ($p < 0.04$). At multivariate regression analysis (Cox model) the mean left atrial appendage flow velocity > 33 cm/sec ($p = 0.0018$, OR 3.2, CI 95% = 1.7-5.8), the arrhythmia duration < 6 weeks ($p = 0.032$, OR 5.2, CI 95% = 2.4-14.3), the left atrial diameter (parasternal long axis) < 48 mm ($p = 0.036$, OR 2.3, CI 95% = 1.4-3.9) and pretreatment with antiarrhythmic drugs ($p = 0.04$, OR 2.4, CI 95% = 1.4-4.1) were independent predictors of cardioversion success.
Conclusions: In patients with persistent nonvalvular atrial fibrillation, measurement of left atrial appendage peak emptying flow velocity by transesophageal echocardiography before electrical cardioversion provides valuable information for prediction of cardioversion outcome. In transesophageal echocardiography guided management of atrial fibrillation, assessment of left atrial appendage velocity profile can be easily incorporated into pre-cardioversion echocardiographic examination.

P1579 External direct current cardioversion in atrial fibrillation – Efficacy and outcome in a consecutive patient cohort

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External direct current Cardioversion (DC-CV) after suitable preparation (sufficiant anticoagulation or TEE) is an effective and low risk intervention for treatment of atrial fibrillation (afib). The outcome is dependent on numerous clinical variables.
Methods In 262 of 1307 consecutive afib patients (pts) included during a 2-year prospective registration in the Brandenburg Atrial Fibrillation Registry DC-CV was the treatment of choice. This was performed during 327 admissions.
Results Of 327 hospital stays within which DC-CV was required, 215 admissions electively, 91 because of acute afib symptoms and 21 because of other cardiac or non-cardiac diseases.
Primary successful DC-CV was achieved in 307 cases (94%). Success rate was 92% in those 180 pts with persistent afib of more than 1 month.
Early relapse occurred in 36 cases (12% of primarily successful converted pts), 1/3 within few sinus beats. 271 (83%) were discharged in stable SR (chronic afib: 152 pts, 78%), 162 (60%) of them with additional beta-blocker medication, 60 (22%) with specific antiarrhythmic drugs (others: no drugs for prevention of relapse).
Late recurrence requiring hospitalization for DC-CV occurred in 48 pts (65 stays) after a median of 85 days. Relapses in ambulant pts are subject of ongoing follow up.
Conclusion The vast majority of pts, even with chronic afib, could be cardioverted successfully and discharged from hospital in stable sinus rhythm.
Readmission to hospital because of relapse requiring DC-CV was necessary in a minority after a median of 85 days and was, thus, accepted by most pts as a reasonable therapeutic concept.

P1580 The relation between left atrial function and acceleration slope of mitral A wave after cardioversion in patients with acute atrial fibrillation

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Purpose: After cardioversion of AF to sinus rhythm, atrial stunning occurs and it takes atrial function a few weeks to recover and precise determining of this period still associated with increase in the risk of thromboembolism is important to continue anticoagulation. This study was planned to evaluate the relation between the left atrial (LA) function and the acceleration slope (Acc-S) of mitral A wave after restoration of the sinus rhythm (SR) in patients with an acute lone atrial fibrillation (AF) attack.
Methods: Thirty patients (52±18 years, 19 female) with a lone AF attack were enrolled in the study. The SR was restored by the electrical cardioversion in 6 patients, the pharmacological cardioversion in 20 and spontaneously in 4. Echocardiographic examination was performed at the first and 30th days after restoration of the SR. The ejection fraction of the LA obtained by end diastolic and pre-p wave volumes of the LA was taken as reference method to determine the LA function. The mitral A velocity and its Acc-S were measured by placing PW Doppler sample volume at the tips of mitral leaflets.
Results: There were no differences for mitral A velocity (76±21 vs 80±21 cm/sec), the LA diameter (38±8 vs 38±7 mm) and end diastolic volume of the LA (32±33 vs 29±22 cm^3) between first and 30th day examinations whereas pre-p wave volume of the LA (28±19 vs 37±16 cm^3, p=0.03), the Acc-S (910±406 vs 1041±401 cm/sec, p= 0.01) and the ejection fraction of the LA (37±15 vs 52±22%, p= 0.008) had statistically significant differences. There were significant correlations between the Acc-S and the ejection fraction of the LA for both first ($r=0.67$, $p<0.001$) and 30th days ($r=0.74$, $p<0.001$).
Conclusion: The acceleration slope of mitral A wave was found to be closely related with the LA function in patients who have been converted to SR after AF. Thus it may be a new parameter to evaluate the LA function in clinical use.

P1581 Immediate haemodynamic effects of effective internal cardioversion in chronic persistent atrial fibrillation

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The aim of this study was to assess the immediate hemodynamic effects of sinus rhythm (SR) restoration by transvenous internal atrial cardioversion (CV). in chronic persistent atrial fibrillation (AF).
Fifty patients with chronic persistent AF (mean arrhythmia duration= 8.9±9.0 months, range 1-48) were enrolled and in 12 of them no underlying structural heart disease (HD) was detectable. Internal CV was performed after a wash out from antiarrhythmic drugs. Before CV and 15 min following restoration of stable SR, hemodynamic parameters were obtained using a Swan-Ganz thermodilution catheter.
Results: SR was restored by internal CV in all the patients, with a mean delivered energy of 5.8±3.2 joule (range 1.2-15.7). In patients with structural HD (n=38) restoration of SR was associated with a significant reduction in heart rate (HR) (from 92±19 to 72±14 bpm, $p<0.001$), a significant increase in cardiac index (CI)(from 2.09±0.51 to 2.22±0.55 $l/m/m^2$, $p<0.03$) and a significant increase in stroke work index (SWI) (from 24±10 to 32±12 $g.m/m^2$, $p<0.001$), with a reduction in pulmonary capillary wedge pressure (PCWP) of borderline significance. In patients without structural HD (n=12) restoration of SR was associated with a significant reduction in HR (from 103±23 to 74±9 bpm, $p<0.005$) and a significant increase in SWI (from 27±8 to 36±9 $g.m/m^2$, $p<0.02$); no significant changes was observed in CI (from 2.42±0.48 to 2.43±0.45 $l/m/m^2$, n.s.) and PCWP.
In conclusion, restoration of SR in patients with chronic persistent AF results in an immediate improvement of systolic function in patients with structural heart disease. In patients without structural heart disease this improvement is less noticeable.

P1582 The factors influencing recurrence of atrial fibrillation after cardioversion

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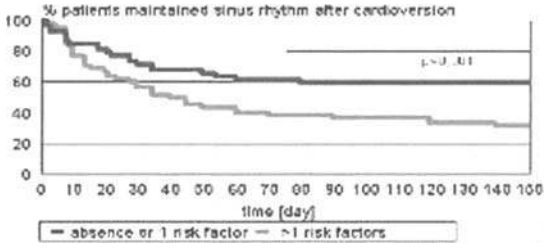
Background: Factors which predict the maintenance of sinus rhythm (SR) after cardioversion in atrial fibrillation (AF), have not been well defined. There is few data concerning the impact of the recovery of the left atrial mechanical function (r.l.a.m.f.) on AF recurrence. The aim of the study was to identify the clinical and echocardiographic predictors for the recurrence of AF.

Methods: 112 consecutive pts mean age 62,1 yrs, after electric or pharmacological cardioversion were divided into: I gr. n=50 maintained SR during 6 months follow up and II gr. n=62 with the recurrence of AF. The clinical examination and 2D ECHO Doppler were performed. From Doppler mitral flow the r.l.a.m.f. at 1st day after cardioversion was evaluated.

Results: No significant relation was found between two groups in respect to age, sex, aetiology, duration of AF, left atrial size and ejection fraction. In univariate analysis the lack of r.l.a.m.f. at 1st day (relative risk rr=1,15, p<0,01), the functional NYHA class II-III (rr=1,86, p<0,005) and the history of AF episodes (rr=2,02 p<0,0005) were identified as predictors for recurrence of AF. In multivariate analysis using Cox proportional hazard model the above 2 factors remained independent also irrespectively of the therapeutic approach.The Kaplan-Meier analysis has shown that out of all analysed risk factors the most significant were functional NYHA class, history of AF and the lack of r.l.a.m.f. The Kaplan-Meier curves computed for selective risk factors - test log-rank (figure).



Conclusion: The history of AF, functional NYHA class II-III and the lack of r.l.a.m.f. seem to be independent predictors for recurrence of AF. The presence of more than 1 risk factor failed the maintenance of SR during 6 months follow-up.

P1583 Cardioversion of atrial fibrillation – Clinical results

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Background: Treatment with DC-conversion (DC) for persistent atrial fibrillation (AF) includes a substantial risk för relapse. This risk has been demonstrated to be related to certain clinical risk factors. However, the risk and the risk factors have mainly been determined from controlled trials, including highly selected patients that does not mimic the clinical population with AF. Also, the duration of pharmacological antiarrhythmic treatment after DC varies in different studies.

Aim and methods: We wish to demonstrate the treatment effect of AF in all referred patients - only exclusion criteria was contraindication for anticoagulant (AC) treatment - mainly utilizing one treatment modality: 3 weeks of AC-treatment followed by 4 weeks of additional amiodarone treatment (400 mg OD). Then DC followed by 3 months of AC and amiodarone (200 mg OD) treatment. The patients were then re-referred to the primary practicians. These patients includes all planned DC in Malmö, a Swedish city with 250.000 inhabitants.

Patients: 351 patients were included. Mean age is 72 (range 29-92) years. 65% are males. 21% has performed earlier DC (mean 2,0, range 1-2) and the duration of AF is 12,6 (range 3-240) months. LVEF is (mean) 0,46 (range 0,15-0,70). 21% has LVEF < 0,35. The mean atrial diameter is 69,3 (range 52-110) mm. 14% have diabetes mellitus, 38% hypertension, 36% heart failure and 9% significant valve disease.

Results: Amiodarone treatment could be given to 73% of the 351 patients. Remaining patients received Sotalol or no antiarrhythmic treatment. 13% had thyroid disease. 79% of the patients regained sinus rhythm (SR)following the DC. After three months 60% were still in SR, while 6% har intermittent AF. 12 months after the DC 45% had SR. Between 3 and 12 months did 45% receive betablockers, and 10% digoxin. The only risk factors for relapse were duration of AF (P<0,05) and gender (P<007).

Conclusions: A time-limited treatment with an effective antiarrhythmic drug (amiodarone) combined with DC was highly effective in the treatment of patients with AF, comparable to the results from clinical trials with selected patients. Patients with AF-duration less than 3-5 years had the highest success-rate. Other traditional risk factors for relapse had no influence on the results.

INFLAMMATION IN ATHEROSCLEROSIS

P1584 Met-RANTES (chemokine receptor antagonist) treatment reduces atherogenesis

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Recruitment of mononuclear leukocytes (macrophages and T lymphocytes) within atherosclerotic lesions is a critical feature of the chronic inflammatory and fibroproliferative response central to atherosclerosis. Attraction of leukocytes to tissues is controlled by chemokines, which has been implicated during atherogenesis. Besides MCP-1, the chemokine RANTES has been detected within atherosclerotic lesions. RANTES interacts at least with the chemokine-receptors CCR1, CCR3, CCR5 and has been implicated in several infectious diseases, during rejection following organ transplant, or arterial injury.In addition, we demonstrated that the chemokine analogous antagonist Met-RANTES (Met-R) inhibits leukocyte chemotaxis in vitro. Therefore, we decided to investigate if Met-R treatment could influence the progression of atherosclerosis in vivo.

LDLR-/- mice fed a high-cholesterol diet were divided in 3 groups (n=8 per group): controls, Met-R treatment (100μg) or saline treatment (100μl) twice/week intra-peritoneally. Animals were sacrificed after 12 weeks of treatment. Atherosclerotic lesion progression was determined by computer image analysis measuring the extent of sudanophilic lesions within the abdominal aorta and aortic root. Serum lipid profiles and body weight did not differ between groups.

Treatment with Met-R significantly reduced the progression of atherosclerosis within abdominal aorta and aortic root compared to controls. For the abdominal aorta, the lipid deposition in controls, saline and Met-R group were 16±1%, 15±1.5%, and 7±2%, respectively (p<0.05). Similar results were obtained in aortic root analysis.

To our knowledge, this is the first demonstration that blocking chemokine pathway by treatment with a chemokine analogous antagonist limits the progression of atherosclerosis in vivo. Knowing the important role of inflammation during atherogenesis, these findings indicate that blocking chemokine receptor/ligand interactions may provide novel and effective therapeutic strategies to reduce the evolution of this common disease.

P1585 The prognostic value of C-reactive protein in patients with intermediate coronary lesions and a normal fractional flow reserve

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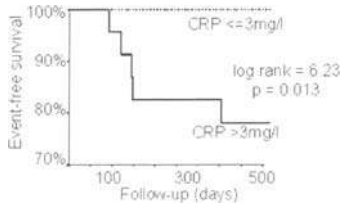
Aim: To assess the prognostic value of plasma C- reactive protein (CRP) in patients with intermediate coronary lesions (diameter stenosis (DS) 40-70%) who were deferred from angioplasty based on a FFR of >=0.75.

Methods: Pre procedural plasma levels of C-reactive protein were measured in 55 patients with stable angina undergoing cardiac catheterization for an intermediate coronary lesion with a mean DS of 53%(range 42-69%). Maximum hyperemia was induced by 15-20 mcg i.c. adenosine to determine FFR defined as the ratio of mean distal coronary pressure to mean aortic pressure during maximum hyperemia. Patients were followed for one year to document major adverse cardiac events (MACE; cardiac death, myocardial infarction, CABG, PTCA).

Results: During a mean follow up time of 323±17 days 5 cardiac events occurred (9.1%; 2xCABG, 3xPTCA). Initial DS (58±7% vs. 53±8%) and FFR (0.86±0.07 vs. 0.85±0.07) were not different between the groups with and without MACE. However, CRP was significantly higher in the group with compared to the group without MACE (median; 6.0 mg/l, range; 4,7-42,4 vs. 1,8 mg/l, 0,20-16,0, p=0.002). DS (53±2% vs. 52±2%) and FFR (0.84±0.11 vs. 0.86±0.15) were not different between patients with a CRP >3mg/l compared to patients with a CRP <=3mg/l. The survival curve below shows the increased risk for coronary events for patients with a CRP>3mg/l.



The Kaplan-Meier survival curve.

Conclusions: A normal C-reactive protein is strongly associated with uncomplicated follow up in patients with hemodynamic non-significant coronary lesions. Plasma levels of C-reactive protein adds additional information for optimal risk stratification in patients with intermediate coronary lesions.

P1586 C-reactive protein: associations with traditional cardiovascular risk factors among young, healthy Polish men

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Objective: Several prospective epidemiological studies have demonstrated that inflammatory markers such as C-reactive protein (CRP) are predictors of future coronary events among apparently healthy men and women. The purpose of this study was to determine serum levels of CRP and their associations with traditional risk factors of atherosclerosis in population of young, healthy Polish men.
Methods: In 150 men (mean age 20,5±1,2 yrs) we evaluated clinical (age, history of smoking), anthropometric (body mass index-BMI, waist to hip ratio-W/H, arterial blood pressure-BP) and biochemical measurements (CRP, total cholesterol-TC, HDL-cholesterol, LDL_cholesterol by Friedwald's equation, triglycerides-TG, uric acid-uric, apolipoprotein A- apoA, apolipoprotein B-apoB and glucose-glc).
Results: In studied group there were a positive correlation between the levels of CRP and values of W/H ratio (r=0,20; p=0,05) and negative correlation between the levels of CRP and HDL-cholesterol (r= -0,21; p=0,05) as well as apo A (r=-0,34; p=0,05).

Studied parameters	mean	SD
CRP (mg/dl)	0,135	1,2
BMI (kg/m^2)	22,93	2,2
W/H	0,88	0,07
BP sys (mmHG)	131,4	14,5
BP dia (mmHG)	75,3	8,3
TC (mg/dl)	72,8	29,9
HDL-chol (mg/dl)	56,1	10,6
LDL-chol(mg/dl)	98,4	25,9
TG (mg/dl)	95,7	46,8
Uric (mg/dl)	4,8	0,8
Apo A (mg/dl)	1,64	0,21
Apo B (mg/dl)	0,77	0,18

Conclusions: CRP levels were associated with several risk factors of atherosclerosis (W/H ratio, HDL-cholesterol, apo A) which are regarded as parts of insulin resistance syndrome (IRS) which is of great importance role of pathogenesis of atherosclerosis. Our data suggests the potential role of inflammation in the pathogenesis of IRS.

P1587 The proatherogenic effects of C-reactive protein are mediated via endothelin-1 and interleukin-6 production: a novel observation

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Background: C-reactive protein (CRP) is one of the most powerful predictors of myocardial infarction, stroke, and vascular death currently known. In addition to predicting adverse cardiovascular events, CRP has been suggested to actively participate in lesion development by inducing a variety of pro-atherogenic processes. In the present study, we examined the role of the potent endothelium-derived vasoactive factor endothelin-1 (ET-1) and the inflammatory cytokine interleukin-6 (IL-6) as mediators of CRP induced adhesion molecule expression, chemokine production and macrophage low-density lipoprotein (LDL) uptake.
Methods and Results: Study 1: Human saphenous vein endothelial cells (HSVECs) (n = 7 per group) were incubated with human recombinant CRP (25ug/ml, 24 hours) and the expression of vascular cell adhesion molecule (VCAM-1) and intracellular adhesion molecule (ICAM-1) were evaluated by flow cytometry.
Study 2: HSVECs were incubated as described above and the secretion of the monocyte chemoattractant chemokine-1 (MCP-1) was determined by ELISA.
Study 3: Monocytes were isolated from human blood and transformed into macrophages. CRP/LDL uptake was assessed by flow cytometry using immunofluroscent labeling of CD32 and CD14. In each study, the effect of endothelin antagonism (with Bosentan) and IL-6 inhibition (with monoclonal anti-IL-6 antibodies) was examined.
Study 4: The effects of CRP on the secretion of ET-1 and IL-6 from HSVECs were evaluated using ELISA.
Incubation of HSVECs with recombinant human CRP resulted in a marked increase in ICAM-1 and VCAM-1 expression ($p<0.001$). Likewise, CRP caused a significant increase in MCP-1 production, a key mediator of leukocyte transmigration ($p<0.001$). CRP caused a marked and sustained increase in native LDL uptake by macrophages ($p<0.05$). These pro-atherosclerotic effects of CRP were mediated, in part, via increased secretion of ET-1 and IL-6 ($p<0.05$) and were attenuated by both Bosentan and IL-6 antagonism ($p<0.01$).
Conclusions: CRP actively promotes a pro-atherosclerotic and pro-inflammatory phenotype. These effects are mediated, in part, via the production of ET-1 and IL-6 and are attenuated by mixed ETA/B receptor antagonism and IL-6 inhibition. Pharmacological interventions, such as Bosentan, may be useful in decreasing CRP mediated vascular disease.

P1588 Correlation of soluble cell adhesion molecule expression and heat production of atherosclerotic plaques

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Background: Several studies have shown that inflammation plays an important role in the pathogenesis of coronary artery disease. Cell adhesion molecules are critical indicators of the inflammatory process. Recently ex vivo and in vivo studies demonstrated that atherosclerotic plaques show substantially warmer regions. Therefore, the aim of the present study was to measure the luminal surface temperature in patients with coronary artery disease (CAD) and to correlate it with the soluble cell adhesion molecules in order to discriminate the role of inflammation in heat production in acute coronary syndromes. Methods: Twenty-five patients were studied with CAD (12 with myocardial infarction during the last month and 13 with unstable angina) and 10 sex- and age-matched controls without CAD, by measuring plasma levels of soluble inter-cellular adhesion molecule-1 (ICAM) and vascular cell adhesion adhesion molecule (VCAM-1). Intracoronary temperature was measured with a thermography catheter developed in our Institution: a thermistor probe with a temperature accuracy of 0.05 °C, was attached at the distal end of a long 3F polyurethane shaft. Thus, the median temperature differences (TD) at the site of the lesion from the core temperature was measured. Results: It was found that the median TD at the site of the lesion from the core temperature was increased in patients with unstable angina (0.59±0.19 °C) and myocardial infarction (0.27±0.16 °C) ($p<0.001$). Furthermore, a good correlation was observed between levels of VCAM with TD($r=0.53$, $P=0.01$). Also, a correlation with ICAM was also observed without however reaching statistical significance. Conclusion: Local heat at the site of lesion is increased in patients with acute coronary syndromes and may arise from an aggressive inflammatory response occurring in these situations. Accordingly, temperature measurement of culprit lesions may be used in future studies to evaluate the effect of anti-inflammatory regimens on the atherosclerotic plaque.

P1589 Estimation of macrophage infiltration by the local angioscopic findings and vascular flow reserve

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Background: Macrophage infiltration appears to play an important role in plaque instability which occurs in acute coronary syndrome. Recent advances in angioscopy and the use of velocity guide wires can now accurately estimate vessel vulnerability. However, the grade of macrophages infiltrations has not yet to be well elucidated based on the angioscopic (AS) findings and vascular flow reserve (VFR). The aim of this study was to investigate whether the grade of macrophages infiltrations on the AS findings and significance of any changes on VFR.
Methods: We fed the New Zealand white rabbits a diet containing 1% cholesterol for 8 weeks as the control group (n=10). We induced an injury to produce the plaque lesion in the middle abdominal aorta (AA) of these rabbits using a 2F Fogarty balloon catheter as the untreated group (n=10). Further, we treated these rabbits by ramatroban (a TXA2 receptor antagonist; 10mg/kg/day) as the treated group (n=10). The morphology of plaque lesion in the AA was evaluated by 0.018-inch angioscope (6000 pixels). AS findings were classified into 2 groups (protruding or smooth). The VFR was evaluated by 0.014-inch Doppler guide wire (15MHz) for 30 seconds occlusion of the AA using a 2F Fogarty catheter. The VFR was provided by the average peak velocity (APV; cm/s) and was expressed as the ratio of basal to peak APV following reactive hyperemic response. After proceedings, the rabbits were sacrificed and the macrophage obtained from AA sections were stained with antibodies against the rabbit macrophages (RAM-11). The density of total macrophages was quantified into absolute areas of RAM-11.
Results: The macrophage cell densities in the observed lesion was the highest in the untreated group (70 ± 12%) comparing with the treated (30 ± 18%, $p< 0.05$) and control group (10 ± 12%, $p<0.01$). The values of VFR was the lowest (1.3 ± 0.4) in the untreated group comparing with the treated (2.0 ± 0.7, $p<0.05$) and control group (2.4 ± 0.5, $p<0.01$). Further, the incidences of protruding plaques were the most prominent in the untreated group (70 ± 15%) comparing with the treated (20 ± 5%, $p<0.05$) and control group (10 ± 15%, $p<0.01$).
Conclusion: This study clearly shows that the plaque lesions in rabbits AA were composed mostly by macrophage with protruding appearances. These lesions were reduced in the vascular functions. The treatment by RAMA was proved to stabilize these lesion.

P1590 Potential involvement of secretory phospholipase A2 activity in atherosclerosis. Correlation with the dyad CD40/CD40L

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Background: Acute coronary events commonly result from thrombosis triggered by disruption of an atherosclerotic plaque. Migratory immune cells, including activated macrophages and T lymphocytes, are the key cellular elements at all stages of atherosclerosis and abound a sites of plaque rupture. The development of a new concept of assessing the pathogenesis of atherosclerosis in the context of immune-inflammation in the vascular wall open new vistas for the comprehension and treatment of this disease, but the mechanism underlying this network are widely unknown.
Recent reports have pointed to the dyad CD40-CD40L as a stimulus for atheroma-associated cells. This system is a key mediator of cell communication in the immune system. Although originally was defined on B and T cells, recently has been reported that vascular cells, endothelial cells and macrophages can express functional CD40L as well as its receptor CD40, in vitro and in atherosclerotic plaques.
Result: To elucidate the regulatory biochemical pathways involved in the progression of the vascular lesion, we have studied the effect of type II secretory phospholipase A2 (sPLA2) on the expression and signaling of CD40 in the THP-1 cell line. This cell line shows remarkable functional similarities with the macrophages located in the vessel wall that exacerbate the local inflammatory response in the atherosclerotic lesion. We have also compared its effect with the classical proinflammatory citokine TNF-a. The monocitic cells, THP-1, express CD40 functional receptors. Both, sPLA2 and TNF-a treatment increased CD40 expression without affect the levels of CD40L. The cellular response to CD40 engagement includes cytosolic phospholipase A2 phosphorylation, arachidonic acid movilization and increase in the production of MCP-1 and in the expression of Fas/FasL. These effects were enhanced in the presence of sPLA2 and TNF-a. Although, CD40 ligation modulates the expression of the system Fas/FasL does affect neither survival nor cellular cycle and might represent a juxtacrine mechanism of signaling involving other cell types
Conclusions: These data show that sPLA2, besides its effects on the properties of LDL, elicits CD40 expression on macrophages, linking the inflammatory and the immune responses. Another finding from this study is the activation of the Fas-signaling pathway as a mechanism of resolution of inflammation under nonphlogistic conditions.

P1591 Activation of Toll-like receptor 4 by adventitial application of lipopolysaccharide augments neointima formation in a mouse model

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Background: Previously, we demonstrated that the Gram-negative bacterium Chlamydia pneumoniae is frequently present in the adventitia of atherosclerotic arteries. Lipopolysaccharide (LPS) is the principal constituent of Gram-negative bacteria that is recognized by the innate immune system. Toll-like receptor 4 (TLR4) is the transmembrane receptor for LPS signaling. We recently demonstrated TLR4 expression in adventitial fibroblasts. Activation of adventitial fibroblasts induced the up-regulation of various cytokines. In the present study we hypothesized that adventitial application of LPS augments neointima formation in an in vivo situation and that TLR4 is involved in this process.
Methods: To study the effect of adventitial LPS application on the augmentation of neointima formation induced by a cuff, a non constrictive polyethylene cuff (ID 4mm, OD 8mm) was placed around the right femoral artery of wild type BALB/c mice. Gelatin with (n=9) or without (n=9) LPS (1μg/μl) was injected between the cuff and the artery. To study the role of TLR4 in the augmentation of neointima formation by adventitial LPS application, a cuff was placed around the right femoral artery of TLR4 defective BALB/c mice. Gelatin with LPS (n=8) was injected between the cuff and femoral artery. All mice were sacrificed after three weeks follow up.
Results: The wild type BALB/c mice treated with LPS-gelatin showed a significant larger neointima formation compared to wild type BALB/c mice only treated with gelatin: Intima(μm^2), 9134±5144 and 2353±3228 (p=0.003), respectively; intima/media ratio, 0.95±0.51 and 0.22±0.27 (p=0.002), respectively. The TLR4 defective BALB/c mice treated with LPS-gelatin showed a significant smaller neointima formation compared to the wild type BALB/c mice treated with LPS-gelatin: intima(μm^2), 3859±2556 and 9134±5144 (p=0.012), respectively; intima/media ratio, 0.46±0.30 and 0.95±0.51 (p=0.021), respectively.
Conclusions: Adventitial application of LPS augments neointima formation induced by a cuff and TLR4 is involved in this process. These results provide a possible link between adventitial inflammation and arterial obstructive diseases.

P1592 Plasma levels of sCD40 ligand predict the presence of lipid pool in human carotid plaque: an in-vivo study using high-resolution MRI

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Introduction: Large lipid pools and thin fibrous caps characterize vulnerable plaque. CD40 ligand mediates several processes important in atherogenesis and the formation of high-risk plaque, and soluble CD40 ligand predicts risk of cardiovascular events prospectively.
Methods: We tested the hypothesis that plasma levels of soluble CD40 ligand (sCD40L) correlate with evidence of intra-plaque lipid on high-resolution carotid MRI. This study enrolled 41 outpatients with stenoses greater than or equal to 30% in either internal or common carotid artery by carotid ultrasonography (January 2001 to January 2002). All patients had a blood sample drawn, and underwent high-resolution MRI of the carotid arteries. A blinded study radiologist determined the presence or absence of intra-plaque lipid, based on the loss of signal between the TE 20 and TE 55 fast spin echo images. Plasma levels of sCD40L were measured by ELISA. The study was approved by the Human Research Committee of Brigham and Women's Hospital and written informed consent was obtained from all study participants.
Results: The 41 patients had a mean age of 70.0 years ± 8.4, 63.4% were male, 31.7% were diabetic, 80.5% had hypertension, and 12.2% were current smokers. Plasma levels of sCD40L in patients with evidence of intra-plaque lipid (n=13) exceeded those in patients without intra-plaque lipid (n=28) (median 2.57ng/ml, inter-quartile range (IQR) [2.01-3.52] vs 1.62ng/ml, IQR [1.21-2.47]; p=0.03). The relative risk for intra-plaque lipid associated with above median levels of sCD40 ligand compared to below median levels of sCD40L was 5.5 (p=0.046). Adjustment for diabetes, hypertension, smoking status, and ratio of total cholesterol: high-density lipoprotein cholesterol, did not change the magnitude of the predictive effect of elevated sCD40L (relative risk 5.1; p=0.10).
Conclusions: Plasma levels of sCD40L may predict patients with features suggestive of high-risk plaque. Interfacing high resolution MRI with studies of inflammation may provide novel insights into the pathogenesis of atherosclerosis.

P1593 A paradoxical increase in the surface expression of various cell adhesion molecules in human endothelial cells after treatment with statins

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By decreasing LDL levels, statins decrease the substrate for LDL oxidation and therefore one of the main triggers of atherosclerosis. Thus, in vivo treatment of patients with therapeutic doses of simvastatin decreases urinary 8-iso-PGF2alpha excretion, an in vivo index of lipid peroxidation (De Caterina R et al, submitted). However, despite the removal of a main triggers for adhesion molecule expression, therapeutic doses of statins do not decrease circulating levels of soluble adhesion molecules such as Vascular Cell Adhesion Molecule-1 (VCAM-1), E-selectin and Intercellular Adhesion Molecule-1 (ICAM-1) (De Caterina R et al, data on file). In order to clarify this apparent paradox we assessed the in vitro effects of one commonly used lipophylic statin, simvastatin, on the induced surface expression of three proinflammatory adhesion molecules, VCAM-1, ICAM-1 and E-Selectin, and on endothelial nitric oxide synthase (eNOS) in human umbilical vein endothelial cells (HUVEC).
Methods: Simvastatin (10-1000 ng/mL), activated in vitro by alkaline hydrolysis, was incubated with HUVEC for 0-24 h, followed by co-incubation with tumor necrosis factor-alpha (TNF), lipopolysaccharide (LPS), or advanced glycation endproducts (AGEs) for further 12 h. After this time, VCAM-1, E-Selectin and ICAM-1 expressions were assessed by cell surface immunoassays (EIA), and eNOS protein levels determined by Western analysis.
Results and Conclusions: Pretreatment with simvastatin increased both the basal and the cytokine-downregulated expression of eNOS. Simvastatin also, slightly but significantly ($P<0.05$), boosted the expression of adhesion molecules induced by TNF, LPS and AGEs, as show in the table.

Adhesion molecule expression

Stimulus	VCAM-1	E-selectin (% of stimulated expression)	ICAM-1
AGEs (200 microg/mL)	153±23*	217±20*	128±10*
LPS (1 microg/mL)	150±10*	130±13*	133±14*
TNF (10 ng/mL)	135±23*	150±23*	130±10*

Adhesion molecule expression in the presence of simvastatin 600 ng/mL. * = $P<0.05$ vs stimulated control without simvastatin

These observations suggest the existence of an adverse pleiotropic effect of simvastatin on endothelial leukocyte adhesion molecule expression, likely counteracted in vivo by the decrease of LDL.

P1594 Interleukin-6 upregulates AT1 receptor gene expression in vascular smooth muscle cells

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Inflammatory processes and the renin-angiotensin system play an important role in the pathogenesis of atherosclerosis. Activation of the AT1 receptor (AT1-R) leads to enhanced synthesis of the pro-inflammatory cytokine interleukin-6 (IL-6), and angiotensin II, AT1-R, and IL-6 are co-localized in atherosclerotic plaques. Therefore, we investigated whether IL-6 itself may influence AT1-R gene expression in vascular smooth muscle cells (VSMC).

Methods and Results: Cultured rat aortic VSMC were incubated with IL-6 for 0-24h. AT1-R gene expression was assessed by Northern and Western blotting. IL-6 (1 nmol/l) led to a significant, time-dependent upregulation of AT1-R mRNA expression to 150±19% of control after 12h incubation. This IL-6 effect was dose-dependent with a maximum at 5 nmol/l. AT1-R expression was also upregulated by IL-6 on protein level. Transcription blockade experiments showed that AT1-R mRNA stability is not altered and that IL-6-induced AT1-R regulation is mediated by transcriptional mechanisms. Co-incubation of VSMC with IL-6 and the specific pharmacological inhibitors wortmannin, LY294002, PD98059, SB203580, AG490, DPI, or genistein revealed that IL-6-mediated AT1-R upregulation involves activation of PI-3-kinase, p38-MAP-kinase, p42/44-MAP-kinase, and JAK2. Angiotensin II-induced production of reactive oxygen species in VSMC was enhanced after pre-incubation with IL-6 for 24h (DCF fluorescence lasermicroscopy).

Conclusions: IL-6 significantly upregulates AT1-R gene expression in VSMC involving PI-3-kinase, MAP-kinase, and JAK/STAT-dependent signal transduction pathways. This interaction of the pro-inflammatory cytokine interleukin-6 with the AT1 receptor may represent an important pathogenetic mechanism in the development and progression of atherosclerosis.

P1595 Risk factors for coronary artery disease in patients with systemic lupus erythematosus

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Background: Coronary artery disease (CAD), major cause of morbidity and mortality in systemic lupus erythematosus (SLE) patients, has a complex risk profile with SLE related and CAD risk factors.

Aims: Risk factors for CAD in SLE patients (pts) were evaluated in a 10 year longitudinal prospective study.

Design: 142 SLE pts fulfilling ARA criteria, 131(94.3%) females, 39 y mean age were divided in group A - 38 (26.8%) pts with SLE and CAD (angina and/or myocardial infarction) and group B - 104(73.2%) pts with SLE without CAD. CAD was documented by ECG, 2D echo, stress test, Th-201 myocardial scintigraphy. Pts were appreciated for CAD risk factors, steroid therapy > 10 mg/day more than 10 years and ELISA serum level for anticardiolipinic antibodies (ACL) > 25 UE/ml. Plasmatic cholesterol determined using a turbidimetric assay (normal plasma level < 200 mg/dl). Statistical analysis using multiple regression.

Results: The incidence of CAD risk factors is significantly higher in group A (table). In group A 25(65.6%) pts had 3 risk factors or more, 18(47.3%) pts with risk profile composed of steroid therapy > 10 mg/day more than 10 years, cholesterol plasma level > 200 mg/dl and ACL > 25 UE/ml.

Risk factors	Gr.A	Gr.B	p value
Cholesterol plasma level > 200 mg/dl	28(73.3%)	32(31.1%)	<0.001
Family history of CAD	12(31.7%)	10(9.8%)	<0.05
Sedentary life style	13(32.8%)	25(24.4%)	<0.1
Obesity	8(21.4%)	12(11.9%)	<0.1
Smoke	7(20.9%)	13(12.4%)	<0.01
Diabetes	6(17.9%)	8(8.4%)	<0.01
Hypertension	10(26.3%)	15(14.5%)	<0.01
Steroid therapy > 10 mg/day > 10 years	37(97.4%)	15(14.9%)	< 0.0001
ACL > 25 UE/ml	19(51.4%)	19(18.4%)	<0.001

Cardiovascular mortality was 7.8% in group A, 10% from total number of deaths, compared to total mortality 2.11% in group B.

Conclusions: In SLE patients chronic steroid therapy > 10 mg/day more than 10 years and increased titers of anticardiolipinic antibodies are additional risk factors for coronary artery disease.

P1596 Pregnancy-associated plasma protein a (PAPP-a) in determination of unstable coronary plaque

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Objectives: The aim of our study was to assess whether elevation of PAPP-A (metalloproteinase used in fetal diagnosis of Down's syndrome) is associated with acute coronary syndromes.

PATIENTS AND METHODS: A total of 114 patients were included into this study: 65 patients with stable coronary artery disease (SCAD), 25 patients with normal coronary angiogram (N), and 24 patients with acute coronary syndrome (ACS; 14 patients with ST segment elevation acute myocardial infarction (STE AMI), 7 patients with non STE AMI, and 3 patients with unstable angina pectoris). Blood samples for determination of troponin I (TI), C-reactive protein (CRP) and PAPP-A were collected at admission and all patients underwent coronary angiography (and percutaneous coronary intervention if necessary).

Results: All baseline, clinical, and demographic data were comparable among the groups. The plasma level of PAPP-A in patients with ACS (26.5 ± 5.93 mIU/L) was significantly higher than in both control groups: SCAD (3.16 ± 0.26 mIU/L, p = 0.0009) and N (2.53 ± 0.25 mIU/L, p = 0.0007). There was no statistically significant difference between the group N and the group SCAD. The value of PAPP-A was independent on entry TI and CRP level;the PAPP-A threshold value of 9 mIU/L had 71% sensitivity and 100% specificity for ACS. In some patients with STE AMI PAPP-A was already elevated even before pozitivity of TI.

Conclusions: Our results suggest that circulating PAPP-A is a promising marker of unstable coronary plaque. Nevertheless further studies are needed to support this hypothesis.

CELLULAR BIOLOGY OF MYOCARDIAL PROTECTION

P1597 Preischaemic infusion of alpha-human atrial natriuretic peptide elicits myoprotection through nitric oxide-protein kinase C dependent mechanism

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Background: Alpha human atrial natriuretic peptide (alpha-hANP) has been prescribed for the patients with heart failure due to its natriuretic and vasodilatory activity. Recent reports suggested that alpha-hANP generates nitric oxide (NO) that is known to be involved in myoprotective mechanisms. In this study, effects of preischemic infusion of alpha-hANP against ischemia reperfusion were evaluated.

Method: Isolated rat hearts were subjected to Langendorff perfusion with buffered Krebs-Henseleit solution and were divided into five groups. Six hearts received 0.1micro-M of alpha-hANP for 10 minutes (HANP), six hearts received 1mM of a NO synthetase inhibitor N(G)-nitro-L-arginine methyl ester (L-NAME) for 5 minutes before alpha-hANP (LNM), six hearts received 0.02 micro-M of a protein kinase C (PKC) inhibitor chelerythrine chloride for 5 minutes before alpha-hANP (CHE), six hearts received 10 micro-M of a cyclic guanosine monophosphate (cGMP) inhibitor methylene blue for 5 minutes before alpha-hANP (MB), and six hearts served as a control with no interventions (CON). All groups were, then, subjected to 20 minutes of global ischemia followed by 120 minutes of reperfusion. LV pressures, coronary flow and concentrations of cGMP in the perfusate were measured throughout the experiments and infarct sizes were detected at the end of experiments.

Results: Alpha-hANP significantly reduced infarct size as compared to control hearts, and this effect was reversed by either LNM or CHE, but not MB (HANP: CON: LNM: CHE: MB, 26.1±2.8: 42.7±2.3*: 39.0±1.6*: 40.0±2.0*: 29.6±2.6%, *=p<0.01 vs. HANP). Alpha-hANP significantly increased cGMP concentrations and this effect was reversed by L-NAME (HANP: CON: LNM: CHE: MB, 1.04±0.13: 0.16±0.7#: 0.27±0.16#: 0.80±0.15: 0.80±0.10%, #=p<0.05 vs. HANP). There was no significant deference among five groups in terms of LV pressures and coronary flow.

Conclusion: These data suggest that a preischemic infusion of alpha-hANP exerts myoprotective effects against ischemia reperfusion possibly through a NO-PKC dependent mechanism, although a NO-cGMP pathway was also activated.

P1598 The protective effect of bradykinin on ischaemic cardiac mitochondria is mediated by B2 membrane receptors

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Bradykinin (BD) interact with the endothelium and induces vasodilatation, in a process that seems to be mediated by the release of nitric oxide. An important part of the positive effects of BD appear to be mediated by B2 membrane receptors.

The aim of our study was to determine, during acute cardiac ischemia, the role of these receptors on the BD-mediated mitochondrial metabolism protection.

We used an ex-vivo global myocardial ischemia model (Lagendorff system). Forty Wistar rat's hearts were divided in 4 experimental groups - A (180 minutes of perfusion, with a Krebs modified solution), B (60 minutes of perfusion with the same solution, followed by 120 minutes of ischemia), C (as in B, but in the presence of BD 0.1 μM) and D (as in B, but in the presence of BD 0.1 μM and a B2 receptor antagonist - D-Arg-(Hyp3, D-Phe7, Leu8)-Bradykinin 100 μM). Cardiac mitochondria were then isolated by differential centrifugation and the activity of complexes I, II-III and IV of the mitochondrial respiratory chain (MRC) was evaluated, using their metabolic substrates (Glutamate/Malate, Succinate and Ascorbate/TMPD). Parameters assessed were: Respiratory Control Ratio (RCR), O2 consumption during state 3 of mitochondrial respiration (S3), Mitochondrial Membrane's Electrical Potential after Phosphorylation (Delta Psi), Phosphorylative Lag Phase (PLP), Energetic Charges (EC) and Enzymatic Activities (EA) of each of the MRC complexes - see table.

Groups/Parameters	BD BD	BD + D-Arg-(Hyp3, D-Phe7, Leu8)- Bradykinin (Group D)	p value (C vs. D)
PLP (Succinate)	239.2±14.8%	135.4±27.7%	p=0.003
PLP (Ascorbate/TMPD)	228.6±48.9%	63.5±5.1%	p=0.004
Delta Psi (Succinate)	1959.3±363%	625.9±296.3%	p=0.01
Delta Psi (Ascorbate/TMPD)	652.3±81.2%	401.9±100.8%	p=0.09

Note: Values are expressed as % of control (Group A).

When compared to the group treated with BD, the one exposed to D-Arg-(Hyp3, D-Phe7, Leu8)-Bradykinin was capable of reverting the BD's positive impact on PLP and on the Delta Psi recovered after a phosphorylative cycle. These results indicate for the first time, in an ex-vivo myocardial ischemia model, that the positive impact of BD on the mitochondrial phosphorylative system is mediated by B2 receptors.

P1599 Involvement of p38 MAPK in ischaemic preconditioning and thyroxine induced cardioprotection

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Background: Previous studies have shown that thyroxine administration is associated with enhanced tolerance of the heart against ischaemia. Furthermore, ischaemic preconditioning (PC) is a well established means of cardioprotection which involves alterations in p38 MAP kinase during the subsequent sustained ischaemia. The aim of the present study was to investigate whether long-term thyroxine administration protects the heart by interfering with mechanisms that are known to be involved in PC induced cardioprotection.

Methods: a. L-thyroxine (T4) was administered in Wistar rats (25μg/100g/day sc) for 2 weeks (THYR), while normal animals served as controls (NORM). Isolated rat hearts were perfused in a Langendorff mode. After an initial stabilization period, NORM and THYR hearts were subjected to either 20 min of zero-flow global ischaemia (I), THYR(I),n=5 and NORM(I), n=5. or to 20 min of I followed by 45 min of reperfusion (R), THYR(I/R),n=6 and NORM(I/R), n=6. b. NORM hearts were subjected to a four cycle PC protocol (3min of I and 5 min of R followed by 3 cycles of 5 min of I and 5 min of R) before 20 min of I only, NORM(PC+I), n=5 or 20 min of I and 45 min of R, NORM(PC+I/R), n=6. Postischaemic recovery of left ventricular developed pressure was expressed as % of the initial value (LVDP%). Total and phospho p38MAPK were measured by Western blot analysis at the end of 20 min of I and at the end of 45min of R.

Results: LVDP% was higher in THYR(I/R) than in NORM(I/R) [61.5 (6.6) vs 42.8 (4.9)], $p<0.05$. LVDP% was also higher in NORM(PC+I/R) than in NORM(I/R) [59.2 (4.6) vs 42.8 (4.9)], $p<0.05$. Phospho-p38 MAPK was 1.9 fold more in NORM(I) than in THYR(I), $p<0.05$ and 3.5 fold more in NORM(I) than in NORM(Pc+I), $p<0.05$. Furthermore, phospho p38 MAPK was 1.7 fold more in NORM(I/R) than in THYR(I/R), $p<0.05$ and 1.25 fold more in NORM(I/R) than in NORM(PC+I/R), p=0.09.

Conclusion: p38 MAPK activation is attenuated during ischaemia both in THYR and in PC hearts and at reperfusion only in THYR hearts, in a parallel fashion to improved postischemic recovery

P1600 Two-dimensional analysis of myocardial protein expression following myocardial ischaemia and reperfusion in rabbits

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Myocardial ischemia and reperfusion injury (MI/R) can be related to leukocyte activation with subsequent release of cytokines and oxygen-derived free radicals. Activation of the complement system has been implicated in the pathogenesis of myocardial ischemia and reperfusion injury. Inflammatory injury will subsequently result in cellular activation and protein synthesis.

In the present study we analyzed the myocardial protein expression and its pattern following myocardial ischemia and reperfusion, with and without complement inhibition with the synthetic serine protease inhibitor FUT-175 known to inhibit classical and alternative complement pathway in a rabbit model of myocardial ischemia and reperfusion (60min I + 180min R). FUT-175 significantly reduced myocardial necrosis, i.e. creatine kinase release which were analyzed for the three groups ($p<0.05$). Similar, histological analysis demonstrated preservation of myocardial tissue injury and reduced leukocyte accumulation following FUT-175 treatment. Further, the myocardial protein expression was analyzed by two-dimensional gel electrophoresis following MI/R in the different groups. The protein patterns were evaluated by means of MELANIE III a computer-assisted gel analysis system. The biochemical identification of the proteins of interest was achieved using nanoHPLC/ESI-MS/MS. On average, 509±25 protein spots were found on the gels. A pattern of 480 spots with identical positions was found on every gel of five animals of each group. We analyzed 10 spots which were significantly altered, by using massspectrometry. Superoxide dismutase and aB-crystallin were identified. We compared sham group vs. vehicle group and vehicle group vs. FUT-175 treated animals. Expression of the two identified proteins decreased by half the amount in the vehicle group when compared to sham treated animals. Treatment with Fut-175 preserved significantly superoxide dismutase and aB-crystallin protein expression when compared to vehicle treated animals.

The results present profound differences in myocardial protein expression after ischemia and reperfusion and following treatment with the complement inhibitor FUT-175. Our results illustrate the application of proteomics to discover possible new therapeutic targets or to detect unexpected effects of pharmacological inhibitors.

P1601 The role of the apoptosome in nitric oxide-induced cardiac myocyte apoptosis

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Nitric oxide (NO) induces apoptosis in cardiac myocytes (CM) through an oxidant sensitive mechanism. However, additional factors modulate the timing and extent of NO effects. We investigated the cytoprotective role and possible targets of c-Jun N-terminal kinases (JNK) in NO-mediated apoptosis. We previously showed that cultured neonatal rat CM exposed to the NO donor S-nitrosoglutathione (GSNO), 1mM) undergo extensive (40-50%) apoptotic cell death beginning at 4 hr after treatment, preceded by strong activation of JNK. In this system, inhibition of JNK strongly enhances and accelerates NO-mediated apoptosis, while constitutive activation of JNK via MEKK1 reduces cell death by 50%. We examined specific effects of JNK inhibition on molecular events in NO-mediated apoptosis by using an adenovirus expressing a dominant negative mutant of JNK1 (Ad-dnJNK). NO appeared exclusively to utilize a mitochondria-dependent pathway for apoptosis, as it did not induce cleavage or activation of caspase-8, with or without JNK activation. Furthermore, NO did not activate cleavage or mitochondrial translocation of pro-apoptotic Bid, a target for caspase-8 and a mediator of cross-talk between the extrinsic and intrinsic apoptotic pathways. However, NO induced a rapid (30 min) translocation of anti-apoptotic Bcl-xL from CM mitochondria to cytosol and a concurrent movement of pro-apoptotic Bad from cytosol to mitochondria. Cytochrome C (cyt c) release from mitochondria permits formation of the ?apoptosome?, a cytosolic complex of cyt c, procaspase-9 and APAF-1 that leads to activation of caspase-9. Consistent with this, NO also induced rapid (10 min) cyt c leakage from mitochondria into cytosol, followed by cleavage and activation of caspase-9 after a lag of 4 hr. Infection with Ad-dnJNK abolished 99% of NO-induced JNK activity, but had no effect on cyt c leakage compared with blank virus-infected or uninfected cells? a Bcl-xL-expressing adenovirus delayed NO-induced cyt c leakage by 12 hr. However, Ad-dnJNK accelerated (by 2 hr) and enhanced (120%) the cleavage and activation of caspase-9. These data suggest that NO activates a mitochondria-dependent apoptotic pathway in CM, and that JNK activation blunts CM apoptosis at the level of the apoptosome.

P1602 Doxazosin induces apoptosis in HL-1 cardiomyocytes

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Background: Doxazosin is an alpha1-adrenoceptor antagonist used in the treatment of essential hypertension, but its administration has been associated with increased risk of major cardiovascular events. A biological mechanism to explain doxazosin's role in increasing cardiovascular disease has not been apparent. Our aim was to investigate a possible proapoptotic effect of doxazosin on cultured cardiomyocytes.
Methods and Results: HL-1 cardiomyocytes is a mouse AT-1 tumor lineage derived cell line that maintains the phenotypic characteristics of adult cardiac cells and yet are able to divide. Hoechst dye vital staining, MTT metabolic activity test, and flow citometry, demonstrated that doxazosin treatment induced apoptosis in HL-1 cardiomyocytes in a time- and dose-dependent manner. Hoechst dye vital staining showed that, at 12h, 10μM doxazosin induced a 42.63±5.04% of apoptosis vs. 22.12±0.97% of control (n=3, $p<0.01$), and higher doses increased dramatically apoptosis (78.96±0.57% at 20μM and 90.10±0.20% at 40μM; n=3, $p<0.001$). At 48h, 1 μM doxazosin increased apoptosis to 34.65±2.07% vs. 21.61±4.22% of control (n=3, $p<0.05$), 10 μM induced 44.49±3.22% of apoptosis (n=3, $p<0.001$), and almost 100% cells were dead at 20 and 40μM (n=3, $p<0.001$). MTT analysis showed a decrease of HL-1 cells metabolic activity as soon as at 12h of 50 μM doxazosin treatment (78.13±7.2% of control, n=3; $p<0.05$). Treatments for 24h with doxazosin decreased MTT activity to 69.21±4.22% of control(n=4; $p<0.05$)at 20μM; 64.5±4.38% of control at 40 μM (n=3; $p<0.001$); and 55.22±4.58% of control at 50 μM (n=3; $p<0.001$). The same pattern was observed at 48 and 72h, with a more dramatic decrease at low doses(47.81±7.23% of control at 20μM; n=3, $p<0.001$). Flow cytometry analysis of HL-1 cells treated with doxazosin revealed an increase of apoptosis consistent with a decrease of S/G2/M cell cycle phase. Exposure to phenoxybenzamine, an irreversible inhibitor of alpha1-adrenoceptors,did not influence the proapoptotic effect of doxazosin in HL-1 cells.
Conclusions: Cardiomyocyte apoptosis induced by doxazosin in HL-1 cardiomyocytes could help to explain the increase of cardiovascular risk associated with this drug.This apoptotic effect of doxazosin is independent of its capacity to antagonize alpha1-adrenoceptors.

P1603 Lack of cardiotoxicity after intracoronary paclitaxel application

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Objective: Use of antiproliferative agents in cancer therapy is frequently complicated by cardiotoxicity. Intracoronary administration of liphophilic agents like taxane compounds is potentially suited for prevention of restenosis in interventional cardiology. The aim of the present study was to evaluate cardiotoxicity of intracoronary administration of the taxane Paclitaxel dissolved in a conventional contrast medium.
Methods: Coronary stents were implanted into LAD and CX arteries of 17 pigs. Io-promide was used in group I (control), the treatment groups were injected with 80 ml intravenous Iopromide plus 12.8 mg Paclitaxel (group II), 80 ml intracoronary Iopromide plus 6.4 mg Paclitaxel (group III), and 80 ml intracoronary Iopromide plus 12.8 mg Paclitaxel respectively (group IV). Left ventricular levocardiography was used to evaluate measures of left ventricular function from the pre-sacrifice angiography at 28-day follow-up.
Results: There were no thrombotic complications and no significant adverse events of ECG, blood pressure or contractility during or after Iopromide-Paclitaxel injections. At follow-up, there were no differences in parameters characterizing global and local left ventricular ejection fraction (see table).

Left ventricular function

	group I	group II	group III	group IV	p
# of pigs	6	3	4	4	
LVEDP [mmHg]	23.2±3.6	24.0±5.3	23.8±1.7	20.5±4.2	0.563
dp/dt [mmHg/s]	1.0±0.3	1.3±0.5	0.9±0.4	1.1±0.2	0.461
LV-EF [%]	38.5±10.2	49.0±12.0	45.5±9.8	46.3±6.2	0.418

LVEDP=left ventricular enddiastolic pressure, LV-EF left ventricular ejection fraction

Conclusion: Intracoronary application of the antiproliferative taxane compound Paclitaxel added to a conventional contrast agent does not induce impaired left ventricular function.

INFLUENCE OF GENE POLYMORPHISMS

P1604 Ethnic differences in beta 2 adrenergic receptor polymorphisms distribution

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Background: Polymorphisms of the beta 2 adrenergic receptor (AR) are important in cardiac physiology and could have a role in the expression of cardiovascular diseases.
Objective: This study investigates distribution of previously identified polymorphisms at three sites within the beta 2 AR gene in the chilean population and compares it to that observed in other populations.
Methods: Three sites within the beta 2 AR gene: the Arg16-Gly, Gln27-Glu and Thr164-Ile alleles were studied. Restriction enzyme analysis of amplified beta 2 AR gene products (PCR-RFLP) was used to analyse the frequency of the Arg16-Gly, Gln27-Glu and Thr164-Ile polymorphisms with the beta 2 AR gene in 165 chilean subjects. The results were compared with the reported prevalence in caucasian and japanaise population.
Results: The frequency of different beta 2 AR alleles in the three population is presented in the table.

Populations	Arg16Arg	Arg16Gly	Gly16Gly	Gln27Gln	Gln27Glu	Glu27Glu
Chilean(n=165)	16%	63%	21%	46%	68%	13%
Japanaise(n=836)	24%	48%	28%	89%	10%	1%
Caucasian(n=212)	16%	45%	39%	32%	53%	15%

There were no significant differences in the polymorphisms distribution at the sites 16 and 164 (not showed). However, the distribution at the site 27 was different between chilean and japanaise population ($p<0.001$). Moreover, in chilean population the proportion of polymorphism Gly16Gly was lower and the Glu27Glu higher than the observed in the caucasian population (p=0.001 and <0.01 respectively). In addition, Glu27Glu was less frequent in the japanaise population. The polymorphism Ileu164 was uncommon in all groups.
Conclusion: There are differences in beta 2 AR polymorphism distribution in the analized ethnic groups. In Chile the lower proportion of Gly16Gly (associated to increased downregulation) is balanced by Glu27Glu polymorphism (absence downregulation).
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P1605 Relation of the G protein beta-3 subunit C825T polymorphism with left ventricular structure and function in a large population sample

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A G protein beta-3 subunit (GNB3) C825T polymorphism results in a truncated splice variant protein that is associated with enhanced transmembrane signaling, increased proliferative activity, and arterial hypertension. The aim of the present study was to further investigate the association of the GNB3 C825T polymorphism with the left ventricular structure and function.
2052 individuals from a large scale population-based sample were investigated for the GNB3 C825T polymorphism as well as anthropometrical and biochemical characteristics including echocardiographic parameters of left ventricular structure and function.
Complete genotyping and echocardiographic data were available in 1720 individuals (829 men and 891 women). The mean left ventricular mass indices in men with CC (n = 384) and TT (n = 84) genotypes were 98.3 ± 1.2 g/m^2 and 100.0 ± 2.8 g/m^2, respectively (p = 0.64). In women, the corresponding values were 83.1 ± 1.0 g/m^2 for the CC genotype (n = 397) and 83.8 ± 2.1 g/m^2 for the TT genotype (n = 91, p = 0.32). Likewise, septal and posterior wall thickness as well as left ventricular dimensions and parameters of the diastolic function were not associated with the GNB3 C825T polymorphism in the entire sample as well as in any of several subgroups, e.g. subjects without antihypertensive medication. Moreover, the C238T allele status was not a significant determinant of serologic markers of left ventricular mass, such as atrial or brain natriuretic peptide. Finally, multivariate analyses failed to show any influence of the GNB3 C825T polymorphism on the parameters of left ventricular structure and diastolic function after adjustment for potentially confounding factors including age, systolic blood pressure, sex, and body mass index.
In conclusion, we were not able to confirm in this large population sample the previously published associations of the GNB3 C825T polymorphism with left ventricular structure and diastolic function.

P1606 No influence of I/D polymorphism of angiotensin-converting enzyme gene on exercise-induced cardiac hypertrophy in teenagers

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Background: Long-term athletic training induces a physiological cardiac hypertrophy. However, similarly trained athletes develop LVM to a different extent, suggesting that genetic factors may modulate heart size. I/D polymorphism of Angiotensin Converting Enzyme (ACE) gene has been associated with exercise-induced cardiac hypertrophy in adults.
Aim of the study was to investigate the influence of I/D polymorphysm of ACE gene in the development of LVM in a group of teenage athletes.
Matherials and Methods. 75 competitive soccer players aged 14 to 18 (mean±DS=15±1,2) were examined by echocardiography (echo) and bioelectrical impedance analysis (BIA).Anthropometric data, body composition and standard echo measurements were compared to mean, lower and upper limits (5th and 95th percentile) of 52 normal controls aged 14 to 18 (mean±DS=15±1,6). ACE genotype was also assessed in all subjects.
Results: Genotype distribution was in agreement with Hardy-Weimberg equilibrium and allele frequency were comparable to those found in controls.Body surface area (BSA) (1,8±0,1 vs 1,7±0,2; p<0,001), fat-free mass(FFM) (58,6±7 vs 52±8,5;p<0,001) and all mean echo measurements (left atrium size 29,3±2,2mm vs 28,3±2,9mm; septal thickness 9,5±0,1 vs 8,5±1;posterior wall thickness 9,5±1,1mm vs 8,3±0,9mm; left ventricular(LV) diastolic diameter 51,4±4,4mm vs 49,4±3,5mm; LV systolic diameter 32,1±3,6mm vs 30±3,3mm; Lvmass 195,3±32g vs 165,3±37,6g; Lvmass/BSA 115,5±18,9g/mq vs 95±18,2g/mq; Lvmass/FFM 3,5±0,5g/Kg vs 3±0,4g/Kg; p<0,001 for all variables) were significantly greater in athletes than in controls.Increased left ventricular mass was found in athletes as a results of increased left ventricular cavity dimension and wall thickness.Left ventricular hypertrophy was found in 17 athletes, but no association was found with ACE genotype (II=41%, DD=41%, ID=18%)
Conclusione. Our results show the adaptative cardiac hypertrophy in response to physical training in a group of homogeneus teenage athletes. It appeares as a moderate and physiological hypertrophy with normal systolic and diastolic functions. In young people, ACE genotype seems to have none influence in the development of LVM.

P1607 Novel BNP C-1563T promotor-polymorphism associated with blood pressure and left ventricular mass

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The cardiac natriuretic peptide BNP (brain natriuretic peptide) is secreted from the left ventricle (LV) in response to increased stretch and has potent vasodilatory and antihypertrophic effects. Recently, a novel C/T-polymorphism (TGA[C/T]ATCA) in the putative cAMP response like element (CRE) of the BNP promoter has been described.
To assess the frequency of this polymorphism as well as the association with blood pressure (BP) and LV mass index (by echocardiography), a total of 2153 subjects (n=1059 female, 1094 male) of two population-based surveys (MONICA Augsburg) were genotyped. The respective frequencies of the genotypes were 93,5% (CC), 5,8% (CT), and 0,8% (**TT**). In subjects with the less frequent genotypes CT and **TT**, systolic BP was significantly lower as compared to subjects with CC (133±22 mmHg vs. 138±21; p<0.003), even in the normotensive (BP<140/90mmHg) subgroup (n=740, CT 119±12 mmHg vs. CC 123±13; p<0.008). Presence of a T-allele was also associated with lower systolic BP after adjustment for age, body mass index, and gender in this subgroup (p=0.02 multivariate, β-coefficient -3,4). Presence of the T-allele was further associated with a significantly lower LV mass index (CT&**TT** 83±19 gr/m^2 vs. CC 88±24; p<0.008), particularly in male subjects (n=717, CT&**TT** 88±19 gr/m^2 vs. CC 96±25; p<0.008; TT 72±25 gr/m^2; p<0.007 vs. CC und p<0,05 vs. CT). The association of the T-allele with lower LV mass index was partially independent from BP and remained statistically significant even after adjustment for age, body mass index, systolic BP and LV function (p=0.02, β-coefficient -6,3).
The C-1563T polymorphism of the BNP promotor is rare. Since the T-allele is independently associated with substantial effects on blood pressure and LV mass in these observational studies, further clinical and functional studies are warranted to investigate the relevance of this genetic variant.

P1608 The 807CC genotype of platelet glycoprotein Ia as a protective factor against recurrent acute coronary syndromes: results of a 5-year follow-up

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Background; Glycoprotein (Gp) Ia/IIa is a heterodimeric membrane complex that mediates platelet adhesion to collagen, inducing platelets to aggregate. Recently, a functional gene polymorphism of the Ia subunit has been reported, consisting in a C807T transition (linked with A873G), associated with a variable expression of the platelet surface receptor. We hypothesized that the lower receptor density associated with the 807CC genotype might protect against recurrent events in patients with acute coronary syndromes.
Methods: 88 patients (14 females, mean age 53 years), who were admitted to our CCU for acute myocardial infarction (MI, n=61) or severe unstable angina (n=27) as first manifestation of heart disease before the age of 65, were followed for a maximum duration of 60 months.
Results: Gpla genotyping revealed 807 CC in 40 patients (46%, 7 females, mean 52 years), 807CT in 38 patients (43%, 7 females, mean 53 years), and 807TT in 10 patients (11%, all males, mean 54 years). Patients with the 807CC genotype, compared to carriers of the 807T allele, showed fewer acute coronary events during follow-up (9 vs 21, OR 0.37, 95% confidence interval - C.I. - 0.15-0.95, p=0.0439) and, in particular, fewer MIs (1 vs 10 events, OR 0.10, 95%C.I. 0.01-0.80, p=0.010). Comparison of Kaplan Meier curves confirmed the data (p=0.0441). Moreover, patients with the 807CC genotype had significantly longer median event-free survivals compared to patients with the 807CT or 807 TT genotype (19 vs 11 months, p=0.040).
Conclusions: These data suggest that, among patients with a first acute coronary syndrome, those with the Gpla 807CC genotype (characterized by a lower collagen receptor density on the platelet membrane) may have a lower risk of recurrent events, in particular MI, and a longer event-free survival compared to carriers of the 807T allele.

P1609 Myocardial gene expression analysis using real-time RT-PCR in paediatric patients – Validation of potential reference genes

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Real-time, fluorescent RT-PCR is a highly sensitive method to quantify gene expression. The choice of a reference gene and the quality of pre-PCR protocols like reverse transcription may markedly influence the validity of this method. Therefore, the different steps of real-time RT-PCR and potential reference genes were systematically evaluated for their applicability on myocardial gene expression analysis in hearts with congenital malformations.
Material: Right ventricular myocardium was taken from 22 patients with tetralogy of Fallot (age 4 months - 18 years) during primary corrective operation (n=18) or secondary operation (n=4).
Methods: The following steps of real-time PCR were separately examined: 1. RNA extraction using TRIzol® and incubation with DNAfree®(Ambion) -> quantification by spectrophotometry, 2. real-time PCR for DNA specific single-copy c-Myc -> measurement of contaminating genomic DNA, 3. reverse transcription -> quantification of cDNA using OliGreen®(Molecular Probes), a fluorescent nucleic acid stain, after pre-incubation with RNAse -> comparison of RNA vs cDNA concentrations (efficiency of RT); 4. real-time PCR using ABI Prism 7700 Taqman® -> determination of copy numbers by standard curves (ranging between 101 and 108 copies per well) of cDNA plasmids (Invitrogen). Several genes were analyzed regarding their validity as reference genes: abelson (ABL), β2-microglobulin (B2M), glyceraldehyd-P-dehydrogenase (GAPDH), hypoxanthine-phosphoribosyl-transferase (HPRT), phorphobilinogen deaminase (PBGD), β-glucuronidase (GUS), calsequestrin 2 (CASQ2), 18S ribosomal RNA (18S) and large ribosomal protein P0 (RPLP0), the latter two being intronless and thus not mRNA-specific.
Results: The efficiency of RT varied from 23% to 104%, emphasizing the importance of cDNA measurement for reference gene validation. PCR proved to have high efficiency (ranging from 83% for CASQ2 to 105% for 18S) and low intra-assay variability (4.9% for ABL to 11.2% for 18S). Sample-to-sample variation of copy numbers related to cDNA content was lowest for HPRT (32%), ABL (35%) and PBGD (36%) and highest for GAPDH (60%).
Conclusions: For quantitative real-time RT-PCR of myocardial tissue in children and adolescents PBGD, HPRT and ABL appear to be the most suitable reference genes. The simultaneous use of several reference genes may be useful.

OXIDATION AND ATHEROSCLEROSIS

P1610 Mechanisms of increased vascular superoxide generation in human coronary arteries from patients with coronary artery disease

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Oxidative stress manifested by increased vascular superoxide generation (O2-) is a characteristic feature of vascular disease states. The predominant source of superoxide in animal models of atherosclerosis is vascular NAD(P)H oxidase, but the sources and importance of increased superoxide generation in human coronary artery disease (CAD) are unknown. We used segments of human coronary arteries to elucidate sources of superoxide generation in human coronary arteries from patients with or without CAD. Methods: Segments of human coronary arteries without atherosclerotic plaque were obtained from freshly explanted hearts of patients with or without angiographic CAD (n=14 in each group; matched for sex and age). Vascular superoxide generation was measured using both lucigenin enhanced chemiluminescence (LGCL; 5μM), by SOD-inhibitable ferricytochrome c reduction, and by dihydroethidium (DHE; 2μM) staining. The presence of the NADPH oxidase p22phox and p67phox subunits were evaluated by Western blotting.

Results: Both LGCL and DHE staining indicated that basal superoxide production was greater in coronary arteries from patients with CAD. Superoxide production was localised predominantly in the endothelium and the media. NAD(P)H oxidase inhibitors diphenyliodonium (10μM) and apocynin (1mM) greatly inhibited superoxide generation whereas other oxidase inhibitors had only modest or no effect (Table 1). NADPH and NADH greatly increased superoxide production. NAD(P)H oxidase activity measured in vascular homogenates was also significantly higher in CAD (11±3 vs 5.3±1 RLU/sec/mg protein; p=0.02). Immunoblots, normalized against alpha-actin, showed higher levels of p22phox and p67phox protein in coronary arteries from CAD patients.

Table 1. Sources of O2- in coronary arteries

inhibitors:	native	DPI	apocynin	oxypur.	rotenone	indo	L-NAME
CAD	16.9±0.9	4.8±0.5*	5.9±0.7*	14.8±2.4	16.4±1.4	16.9±2.3	19.6±3.0
non CAD	10.8±1.1	3.6±0.4*	4.3±0.7*	10.5±0.5	11.7±0.8	10.8±2.2	15.1±2.9*
p value	0.009	0.3	0.4	0.03	0.03	0.02	0.1

*-p<0.05 vs. native

Conclusions: NADPH oxidase(s) are functionally the most important source of superoxide in human coronary arteries. NADPH oxidase activity and protein levels are increased in coronary arteries from patients with CAD, supporting the role for this oxidase in atherosclerotic endothelial dysfunction in human coronary arteries.

P1611 Superoxide contributes to angiotensin II induced contractions of human resistance arteries

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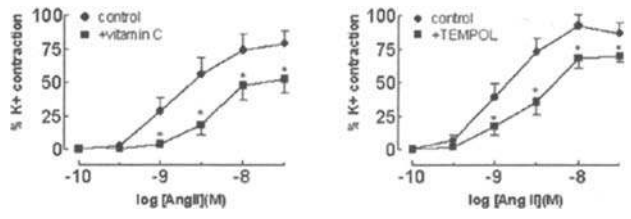
Increased formation of reactive oxygen species (ROS) may contribute to vascular dysfunction. As Ang II stimulates superoxide production in human conduit vessels, we investigated reactivity of human resistance arteries to Ang II and the role of superoxide in this response. Resistance arteries were isolated from biopsies of subcutaneous fat obtained from 15 patients undergoing cardiac surgery (14 male; age 66±3(SEM)yrs BP138/73±4/3mmHg; cholesterol 4.0±0.3mmol/L; 38 vessels). Arteries (239±12μm diameter) were mounted on a Mulvany-Halpern small vessel myograph, set to an internal diameter eqivalent to physiological pressure. Arteries were treated with vehicle, the antioxidant vitamin C (1mM, pH buffered) or the superoxide mimetic TEMPOL (1mM) for 30 min before a single concentration-response-curve (CRC) to Ang II (0.1nM-100nM) was carried out in each tissue. Data is shown as % of initial K^+ contraction and analysed by ANOVA for repeated measures (see Figure; *P<0.05 vs. control). In the presence of vitamin C, both potency of Ang II (pEC50 8.8±0.2 and 8.4±0.1, vehicle vs. vitamin C) and maximum response (80.5±10.3% & 53.5±7.7%, vehicle vs. vitamin C) were reduced (n=8; F=5.54; P=0.03). Decreased Ang II responses were also seen after treatment with TEMPOL (pEC50 8.9±0.1 & 8.5±0.1 (vehicle vs. TEMPOL); maximum 90.2±6.3% & 75.1±7.8% (vehicle vs. TEMPOL); n=9; F=5.93; P=0.03). Decreased potency of Ang II after treatment with vitamin C or TEMPOL is consistent with involvement of prooxidant pathways in the contractile response of human resistance arteries to Ang II. The similar magnitude of the shift of Ang II CRC in the presence of both of these antioxidants supports the concept that superoxide is the major oxidant involved.



Vit C or TEMPOL & Ang II contraction.

P1612 Systemic levels of oxidative stress and title of MDA-autoantibodies in patients with ischaemic heart disease at their first clinical manifestation

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Classical risk factors explain only part of the epidemiological features of atherosclerotic disease. Oxidative stress and immune responses are possibly involved in the onset and progression of atherosclerosis (ATS). Modified lipoproteins and autoantibodies against modified biomolecules have been suggested as other factors that may increase the risk of atherosclerosis, both taken alone or in combination with the classical ones.

Detection of autoantibodies against malondialdehyde-modified low-density lipoproteins (MDA-Abs) has been used as a proof of in-vivo immune response to oxidized proteins. Conflicting results emerged by measurements of plasmatic levels of MDA-Abs in different groups of patients (pts) with coronary ATS.

This study was aimed to compare the titre of MDA-Abs and the plasma levels of malondialdehyde expressed as thiobarbituric acid reactive substances (TBARS) in thirthy male pts with unstable angina (UA) at the time of their first clinical manifestation and in thirty age-matched healthy control subjects (CONTROL).

Pts with UA were characterized by more elevated levels of lipid peroxidation products, when compared to CONTROL group ($p < 0.001$). Plasmatic markers of inflammation (total WBC, fibrinogen) showed a trend for more elevated levels in UA than in CONTROL group.

More patients with UA had high titres for MDA-Abs, when compared to CONTROL group (30% vs 7%, levels over 75° percentile). Out of UA pts, elevated levels of MDA-Abs were not predicted by an increased incidence of traditional risk factors for ATS, by severity of atherosclerosis according to the Gensini score, and had not a consistent association with elevated levels of TBARS.

The results presented here suggest that autoantibodies against MDA seem not to be related with the classical risk factors for ATS. However the potential relevance for MDA-Abs in ATS may be suggested by the observation that out of subjects who had elevated values of MDA-Abs, as defined by a level >75° percentile, mostly were UA pts. Moreover, because increased levels of MDA-Abs were not associated with higher TBARS levels, other determinants to mount an immune response against MDA have to be characterized.

P1613 Levels of oxidative stress are associated with C-reactive protein levels in patients with stable and unstable angina

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Increased formation of reactive oxygen species (ROS) is generally associated with oxidative stress and subsequent cardiovascular tissue injury. Superoxide anion (O2-), and peroxinitrite (ONOO-) have been shown to be implicated in the development of atherosclerosis. It is suggested that some of their functions include upregulation of the redox-sensitive transcription factor NF-kB, an important regulator of inflammatory response.

In the present study we have investigated the levels of ROS in circulating leukocytes, in basal state and after in vitro stimulation, in patients with stable (SA) and unstable (UA) angina pectoris as related to their levels of C-reactive protein (CRP). Twenty-one patients with SA (aged 39-78 yrs; f/m:2/19) and 15 patients with UA (aged 38-79 yrs; f/m: 4/11) were included. Blood samples were drawn in fasting state and analyses of ROS (citrated whole blood) were started within 15 min. Applying flow cytometric techniques, the basal levels and the phorbol 12-myristate 13-acetate (PMA, 100 ng/mL) stimulated production of ROS were measured in circulating granulocytes (Gr). The mean fluorescence intensity (MFI) in 10.000 leukocytes of the fluorochromes dihydroethidium (DHE, 5 mM) and dihydrorhodamine 123 (DHR, 5 mM), reflecting mainly the levels of O2- and ONOO-, respectively, was recorded. When evaluating the PMA-stimulated results, a stimulation index (SI) in which the autofluorescence of the cells and the procedure related influences are calculated, was used.

Results (medians): Levels of CRP were significantly raised in UA vs SA (6.5 vs 2.4 mg/L, p=0.001). Basal levels of O2- and ONOO- in Gr were elevated in UA compared to SA, however not statistically significant (1.75 vs 1.56 MFI and 2.61 vs 2.40, respectively), whereas the SI-levels were significantly lower in UA vs SA (128 vs 192 and 137 vs 195, respectively, p<0.001 for both). Statistically significant correlations were observed between CRP and basal ROS, whereas negative correlations were seen with the SI-levels (CRP vs basal O2-: r=0.462, p=0.005 and vs basal ONOO-: r=0.441, p=0.008; CRP vs SI- O2-: r=-0.408, p=0.015 and vs SI- ONOO-: r=-0.414, p=0.014).

In conclusion: The higher levels of basal ROS found in circulating granulocytes from UA patients as compared to SA patients, significantly associated with the higher levels of CRP, indicate UA patients to be at higher levels of oxidative stress in parallel with increased inflammatory activity. The reduced capacity for in vitro ROS production in UA might indicate that the cells are partly exhausted in this unstable condition.

CONTRAST ECHOCARDIOGRAPHY AND TISSUE CHARACTERISATION

P1614 Cyclic variation of myocardial contrast intensity during real time imaging

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Background: Cyclic intensity variation during real-time myocardial perfusion imaging has been observed in clinical and experimental settings but discrepant results have been reported (systolic vs. diastolic predominance). Aim: We investigated whether cyclic intensity variation is systematically found during real-time perfusion imaging and whether such variations are related to regional contractile function, temporal distribution of contrast intensities or to estimates of capillary blood volume (A) and flow velocity β.

Methods: Real-time Power pulse inversion images were obtained in 14 patients with CAD (3 f, 11m, ages 69±10 years) following i.v. slow bolus injection of 0.7 ml of Optison® and in 12 pigs before, during and after LAD occlusion during continuous infusion of Sonovue (60ml/h). Following bolus injections in patients, instantaneous regional systolic to diastolic (S/D) intensity ratios were calculated when contrast first appeared in the myocardium, before high mechanical index flash and during the subsequent replenishment phase. In animals, A and β were measured in reperfused zones 5 min following release of stenosis and compared to control. Instantaneous S/D ratios were calculated.

Results: In patients, cyclic S/D variation was observed only during the diagnostic window (initial bolus phae: mean S/D: 1.7±2.0 vs. diagnostic phase: septal 1.4±0.3, apical: 1.1±0.3, lateral 1.2±0.3). Cyclic S/D intensity variation was consistently seen throughout early (S/D 1.3±0.7) and late (S/D 1.25±0.7) portions of the replenishment curve. Cyclic S/D variation was not related to regional fractional shortening, nor to the levels of A or β (all r < 0.3, n.s.). In reperfused areas peak A and β and fractional area shortening were lower when compared to control (Arep 5.61±1.0dB; vs. Acontrol 8.6±1.1dB p<0.01) (βrep 0.690±0.095 vs. βcontrol 0.895±0.081; p<0.05; (FAScontrol 30.0±4.3% vs. FASrep 2.3±1.2%; p<0.001). Overall S/D-ratio was > 1 (1.28±0.44, n=645 beats; p<0.001) and stable throughout the replenishment curve. There was no significant difference between S/D-ratio between pre-infarction and reperfusion and between risk area and control area, nor did S/D correlate with FAS (r=0.21), β (r=0.19) and A (r=0.26).

Summary: Cyclic variation of myocardial intensity can be seen with predominant signal intensities during systole. This variation is unrelated to regional function and to estimates of myocardial blood volume and flow velocities. It may relate to contrast distribution, attenuation factors or venular and arteriolar cyclic flow changes ("milking effect").

P1615 Identification of stunned myocardium with real time perfusion image in a Dog Model

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Echocardiographic distinction between stunned and necrotic myocardium can be challenging. Real Time Perfusion Image (RTPI) permits simultaneous assessment of wall motion and myocardial perfusion.

Objective: Evaluation of stunned myocardial by RTPI in an open-chest canine model of ischaemia and reperfusion.

Methods: Seven anesthetized dogs underwent 20 min of left anterior descending (LAD) coronary artery occlusion followed by 180 min of reperfusion. RTPI was performed using power pulse inversion and flash technique (ATL, Bothell, WA), in the apical long axis view. Perfluorocarbon-exposed dextrose albumin (PESDA) injected in bolus was used as contrast agent. Wall motion and myocardial perfusion was analyzed visually at baseline, 20 min of LAD occlusion and after 180 min of reperfusion. Abnormally contracting areas (ACA) and perfusional defects areas (PDA) were calculated by planimetry during diastole. Blood pressure and heart rate were monitored and LAD coronary flow (CF) was measured by electromagnetic flowmeter. After experiment, the hearts were explanted and stained by triphenyltetrazolium chloride (TTC). A p value < 0.05 was considered significant.

Results: At baseline, no contractility or perfusional abnormalities were observed. LAD CF was 22.4+7.52 ml/sec.

	ACA (cm^2)	PDA (cm^2)	CF (ml/sec)
LAD Occlusion (20 min)	5.49 ± 0.79	2.43 ± 0.79	0.32 ± 0.34
Reperfusion (180 min)	4.93 ± 1.03	0.18 ± 0.40	23.62 ± 9.47
p	0.068	0.043*	0.0053*

Values are expressed as mean and standard deviation

TTC confirmed no necrotic areas in all hearts. CF returned to baseline after 180 min of reperfusion.

Conclusion: After a period of ischaemia and reperfusion, RTPI showed that there was a persistence of wall motion abnormality with decrease of perfusional defects in these areas, demonstrating the presence of stunned myocardium. These results could have important implications in the noninvasive diagnosis of coronary artery disease and in the evaluation of myocardial reperfusion procedures.

P1616 Coronary tree assessed with contrast harmonic imaging

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Myocardial contrast echo (MCE) is performed intravenously using intermittent imaging. Recently real time MCE has been possible using third harmonic imaging. Circulation of coronary tree may be visualized at several different levels by changing frame rate, because MCE at different frame rate images coronary flow at different flow velocities. Study population consisted of 20 patients with ischemic heart disease. We performed 3 kinds of MCE, i.e., intermittent, semi real and real time third harmonic imaging using Levovist. 1. Myocardial blood flow velocity and volume were obtained as A and Beta value from TI curve using intermittent imaging (1:1 to 1:8 in pulsing interval). Curve fitting was possible in 76.5% of the targeted ROI (A =5.3±3.8 and Beta =1.0±1.0). Myocardial perfusion image obtained with slow frame rate visualized capillary circulation. 2. Semi real time perfusion image was obtained (frame rate: 5/sec). We observed a cyclic variation of echo intensity in one cardiac cycle in only viable region (Peak intensity: 53±29 AU in end diastole and 33±27 AU in end-systole, p<0.05). This phenomenon may result from the compression of arterioles according to cardiac beat. Myocardial perfusion image obtained with intermediate frame rate visualized pre-capillary (arteriole level) circulation. 3. Real time perfusion image was obtained (frame rate: 26/sec). We observed line form small artery flows in high frame B-mode image in the 80% of viable area. Myocardial vascular image obtained with high frame rate visualized small artery flow. Thus, coronary tree following major epicardial coronary arteries was visualized noninvasively from the small artery to the capillary bed with 3-staged intravenous-MCE in clinical settings.

P1617 Contrast superharmonic imaging: a new specific contrast imaging method

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Background: Second harmonic imaging (2H) has provided a significant improvement in image quality and is nowadays clinically used for both contrast and tissue imaging. However, differentiation between contrast and tissue usually termed contrast to tissue ratio (CTR) is sometimes cumbersome. Super harmonic (SH) imaging is a new technique based on receiving the higher harmonic components of microbubbles. This techniques showed to be more sensitive to contrast by increasing the signal form contrast and suppressing that from tissue (high CTR). To receive the superharmonic components, we developed a wideband transducer containing two types of elements. The total number of elements is 96 and the total bandwidth extends from the fundamental frequency up to the fifth harmonic.
Objective: Determine the clinical feasibility and usefulness of SHI in patients using a contrast agent (Sono Vue®.) for quantification of myocardial perfusion.
Methods: Six patients with various cardiac disease were assessed. Apical four-chamber views were acquired using 2H and SH in triggered mode before and after a bolus injection of 1.0 mL of Sono Vue®. (0.8 MHz, MI = 0.4). Tissue harmonic imaging was determined visually (scale 0-2) and quantitatively using RF processing from regions of interest.
Results: Prior to contrast injection, 2H tissue components were seen in all available segments, whereas the superharmonics were entirely absent. After administration of SonoVue®, myocardial opacification was visualized by SH after contrast entering the myocardium. The total number of segments seen with SH after contrast injection increased significantly to 36 (visual score of 1-2). These scores were confirmed by Rf-data measurements, showing an increase of 10-15 dB in the signal from the bubbles above tissue level. Consequently, using superharmonic imaging, the CTR increased by 5-10 dB compared to 2H imaging.
Conclusion: These preliminary clinical results show two advantages of SHI over 2H: 1. increased CTR with SH and 2. specific imaging of myocardial contrast perfusion. Further studies are underway to determine the clinical value of this promising novel technology.

P1618 Which is the best quantitative method to analyse regional endoepicardial contrast gradient with real-time myocardial contrast echocardiography?

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Background: The optimal way of contrast agent administration and image acquisition in myocardial contrast echo (MCE) is not determined, especially to assess endo and epicardial perfusion, The aim of this study is to perform MCE in endo and epicardium, and to assess accuracy of bolus (B) versus continuous infusion (CI) as well as relative accuracy of different imaging acquisition techniques for real-time MCE comparing it with a standard method (dye-trak microspheres, MS).
Methods: Real-time MCE with coherent contrast imaging (CCI-Acuson-Siemens), a single-pulse cancellation method, was performed in 6 open-chest anaesthetised minipigs, both in basal conditions and after creating a flow-limiting stenosis by reducing LAD flow by 70% of the baseline value. As echo-enhancer, Sonovue, a preparation of sulphur hexafluoride, was used in B (1 ml) and CI (2 ml/min), using low mechanical index (MI) to allow myocardial replenishment after a flash of high MI. In both cases, sequences of 150 telediastolic frames were acquired in endocardium and epicardium of anterior septum (AS) and posterior wall (PW) in short axis view and stored to be processed with propietary software. During continuous infusion, sequences of 200 frames with a temporal resolution of 50-75 ms were also acquired. MCE derived A (peak VDI) and area under the curve (AUC) obtained with the three methods were compared to MS in the same regions of interest(ROI).
Results: Bolus showed the poorest correlation with MS endoepicardial flow ratio (r=0.48, p=0.4 for A endoepicardial ratio and r=0.79, p=0.006 for AUC endoepicardial ratio). Continuous perfusion with telediastolic frame acquisition obtained the highest correlation with MS (r=0.90 p=0.013 for A endoepicardial ratio and r=0.70, p=0.01 for AUC endoepicardial ratio), whereas 50-75 ms acquisition showed a slightly lower correlation with MS (r=0.71 p=0.01 for A endoepicardial ratio and r=0.80, p=0.02 for AUC endoepicardial ratio)
Conclusions: Continuous perfusion of contrast agents seem more accurate than bolus for quantitation of regional endo-epicardial perfusion. MCE performed with continuous perfusion and telediastolic frame acquisition showed an excellent correlation with endoepicardial blood flow ratio.

P1619 Albumin- and phospholipid-microbubbles influence the respiratory burst activity of polymorphonuclear neutrophil granulocytes

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Background: Activated leucocytes that are adherent to the venular endothelial surface can bind and subsequently phagocytose microbubbles that are used for contrast-enhanced ultrasound assessment. The purpose of this study was to investigate whether left heart contrast agents can influence the respiratory burst activity of human polymorphonuclear neutrophil granulocytes (PMN).
Methods: PMN isolated from peripheral blood of healthy volunteers were incubated with albumin- (Optison®) or phospholipid-microbubbles (Sonovue®) for 40 minutes and then stimulated with the bacterial peptide fMLP or with the calcium ionophore A23187. In other experiments priming of PMN was performed using TNF-alpha or the protein kinase C activator phorbol-myristate-acetate (PMA) before incubation with the microbubbles. The neutrophil respiratory burst activity was quantified in both cases photometrically through the superoxide-induced reduction of cytochrome C.
Results: Albumin- and phospholipid-microbubbles (starting at contrast agent concentrations of 2.5-4x105 microbubbles/ml for Optison® and 1-2.5x105 microbubbles/ml for Sonovue®) induced an extensive oxidative response of human PMN to fMLP as well as to the calcium ionophor A23187 (maximum 181±9% for Optison® and 153±5% for Sonovue® for fMLP and 232±6% for Optison® and 199±15% for Sonovue® for A23187). Priming PMN with TNF-alpha or with PMA induced a more extensive oxidative response of human PMN and was possible at 10–fold lower contrast agent concentrations (maximum 227±25% for Optison® and 191±9% for Sonovue® for TNF-alpha and 291±11% for Optison® and 238±17% for Sonovue® for PMA). The effect of both left heart contrast agents on burst activity of PMA activated PMN could be significantly inhibited by preincubation of the cells with the polymerisation-inhibitor Cytochalasin B (63±13% for Optison® and 93±4% for Sonovue®), indicating that phagocytosis contributes to their effect on the burst activity. Soluble human albumin was also capable to provoke a minor but significant stimulatory effect of the respiratory burst activity of PMA activated PMN (maximum 161±7%).
Conclusions: Left heart contrast agents used for contrast-enhanced ultrasound assessment can activate human PMN in vitro inducing an extensive respiratory burst to secondary stimuli. The potential clinical relevance of this effect remains to be elucidated.

P1620 Endocardial delineation in technically difficult echocardiograms by native and contrast-enhanced fundamental,harmonic and pulse inversion imaging

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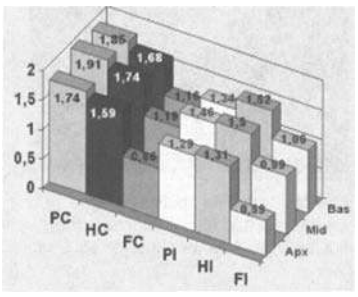
Aim: The visualization of left ventricular endocardial border (LVEB) is essential for echocardiographic assessment of cardiac function. Fundamental imaging(FI) is often insufficient for this purpose. Novel modalities have been applied to improve the echocardiographic LVEB detection but data regarding their comparative value are few.
Methods: Endocardial visualization index(EVI) was studied in a group of 25 patients with insufficient endocardial detection in FI. EVI was defined as the average of individual scores for segments assigned in 3-point scale:0-invisible,1-incomplete,2-complete visualization. FI was directly compared with harmonic imaging (HI), pulse inversion imaging (PI) without contrast and with Optison enhancement (FC,HC,PC resp.) Imaging was performed using ATL 5000HDI and bolus injections of 0.3-0.5ml Optison.
Results: HI and PI improved significantly the visualization of LVEB, however, the addition of contrast provided further improvement, most significant in the studies with poorest quality. EVI values (apical window) for individual modalities were: FI:0,94±0,37; FC:1,17±0,48; PI: 1,34±0,47; HI:1,50±0,37; HC:1,69±0,23; PC:1,86±0,18, each difference significant. HI surpassed PI mainly in the basal segments(fig.1). EVI values in non-enhanced modes from parasternal window were: FI: 1,09±0,84; HI: 1,44±0,80; PI: 1,35±0,80 ($p<0.05$ for HI,PI vs FI; p=NS for PI vs HI).The persistence of contrast effect was 58±49s in FI,116±58s in HI and 157±66s in PI ($p<0.001$ for all).



Conclusions: HI and PI markedly improve the endocardial visualization in difficult echocardiograms. Contrast provides additional benefit in most challenging studies. As opposed to native imaging, in contrast studies PI provides the optimal LVEB delineation.

P1621 Evaluation of left ventricular function in ventilated patients: contrast imaging in comparison with transoesophageal echocardiography

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Background: Echocardiograms done in the Intensive Care Units (ICU) are often suboptimal, especially in ventilated patients. The ICU patients often require an evaluation of their ventricular function. Consequently, a transoesophageal echocardiography (TOE) represents an alternative in order to improve quality of the images. For a few years, the echo of contrast (CE) has made it possible to evaluate the global and regional function among poorly echogenic patients.
Objectives: The study examined the value of contrast echocardiography in the assessment of left ventricular (LV) wall motion in ventilated patients in comparison with TOE.
Methods: Transthoracic echocardiograms were done in 32 ventilated patients. Wall motion was evaluated on standard echocardiography (SE), CE and TOE using a score on a scale of 2 to 0 for each of 16 segments. The segment was assigned a value of 2 if the segment was seen in both systole and diastole, 1 if seen only in systole or diastole, and 0 if not seen at all. A confidence score was also given for each segment with each technique (unable to evaluate; not sure; sure). The EF was estimated visually for each technique, and a confidence score was applied to the EF.
Results: Uninterpretable wall motion was present in 6.1 segments/patient on SE, 1.1 on CE ($p < 0.0001$) and 1.0 on TOE ($p < 0.0001$). An average of 8.7 segments were read with surety on SE, 13.7 on CE ($p < 0.0001$) and 14.5 on TOE ($p < 0.0001$). There was no significant difference for CE vs TOE. Ejection fraction was uninterpretable in 31% on SE, 0% on CE ($p < 0.001$) and 0% on TOE ($p< 0.001$). The EF was read with surety in 51% of patients on SE, 89% on CE ($p < 0.0001$) and 92% with TOE ($p<0.0001$) with no difference for CE vs TOE. Thus, wall motion was seen with more confidence on CE and TOE.
Conclusions: CE gets an equivalent improvement of the image that the TOE. Because CE is less invasive, less expensive and more comfortable than TOE, it should be used in all ventilated patients with suboptimal transthoracic echocardiograms for the evaluation of the LV function.

P1622 Contrast echocardiography for the exclusion of left atrial thrombi in patients with atrial fibrillation prior to cardioversion

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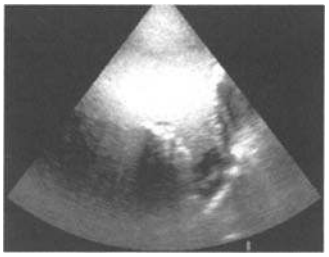
Background: Transesophageal echocardiographic (TEE) guidance of cardioversion in patients with atrial fibrillation (AF) is an alternative method to conventional anticoagulation. Although TEE is considered the gold standard for excluding left atrial (LA) thrombi, in some cases dense spontaneous echo contrast and artifacts may hamper identifying or excluding LA thrombi. Often those patients are refused cardioversion. The purpose of this study was to determine, whether the application of echo contrast (Optison®) facilitates the exclusion of LA thrombi in the latter patient group and may allow for safer cardioversion.
Methods and results: 41 patients with AF and dense spontaneous echo contrast or inconclusive TEE findings were given echo contrast. 14 patients with SR served as controls. Echo contrast completely reduced artefacts in 13 of 22 cases. In 12 of 19 cases with spontaneous echo contrast the LA appendage was completely filled after the application of echo contrast and thus, spontaneous echo contrast was completely suppressed. In 13 of 41 cases it was filled incompletely and in 9 of 41 cases a new mass resembling a thrombus was detected (figure 1). In total in 25 of 41 cases with inconclusive TEE findings an atrial thrombus was definetively excluded. Those patients underwent cardioversion. None of those patients had a cerebral embolic complications as assessed by cranial MR imaging.



Conclusion: The application of echo contrast facilitates the TEE exclusion of LA thrombi and hence improves the safety of TEE guided cardioversion in particular in patients with spontaneous echo contrast.

P1623 Reversible perfusion defects during dipyridamole myocardial contrast echocardiography for the detection of coronary artery disease

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Background: We hypothesized that stress myocardial contrast echocardiography (MCE) technique can detect coronary artery disease (CAD) in the absence of prior infarction on the basis of reversible perfusion defects.
Methods: 55 patients with suspected CAD and no previous myocardial infarction or wall motion abnormality were recruited from 3 centers in Europe. They underwent high mechanical index intermittent B-mode MCE during a continuous infusion of Sonazoid (Nycomed-Amersham) and coronary arteriography (CA) within 1 month of each other. Visual analysis of MCE data and quantitative CA were performed by blinded observers at 2 different centers in the United States.
Results: Forty-two (76%) had ^{3} 50% stenosis of one or more coronary arteries. MCE detected reversible perfusion defect in one or more segment in 83% of these patients. The rate of CAD detection increased with higher degrees of stenosis: 88% in >75% stenosis and 100% in more than 90% stenosis. The specificity for a cut-off <50% stenosis was 44% in this patient population with chest pain. The accuracy of dipyridamole MCE for the detection of >=50% stenosis was 76%.
Conclusion: MCE (using intermittent high mechanical index B-mode imaging) performed very well against quantitative coronary angiography for the detection of CAD in patients without previous infarction or wall motion abnormality. The relatively lower specificity was probably related to selection bias in patients undergoing coronary angiography for chest pain evaluation.

P1624 Dobutamine stress myocardial contrast echocardiography. Intermittent triggering in real-time era

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Purpose: We sought to compare the accuracy of myocardial contrast echo (MCE) methods i.e; intermittent triggered imaging(ITI) versus real-time (RTI) modes in patients undergoing standard high dose dobutamine stress echo (DSE) to rule out ischemia (CAD),validated by coronary angiography.
Methods: After an informed consent,patients undergoing DSE had simultaneous studies in grayscale ITI and Pulse Inversion (PI); and in RTI -in grayscale (PI)®, or pulse inversion Doppler (PPI)®- plus regional wall motion (RWM)studies. Intravenous boluses of Optison® were administered, at rest and prior to peak DSE dose. System settings are outlined in table-1. Off-line interpretation and scoring of myocardial enhancement and RWM was determined by blind review, in 16 segment left ventricle model. Coronary angiography was performed within two weeks of the MCE study. CAD was graded according to visually determined percent luminal diameter stenosis, where 50% and 70% stenoses were taken as cutoff values. Test accuracy and statistical correlation was determined.
Results: Study included 29 subjects. Mean age=57y. A total of 464 segments were each read in 3 methods. 29/29 had ITI & RWM studies. 23/29 in RTI; of whom 14 were in grayscale PI, and 9 in PPI. 16/29 had coronary angiography. Pearson correlation coefficient for global wall motion (WM) & ITI was determined; $r = 0.83$, $p<0.0001$ and for global WM & RTI: $r = 0.86$,$p<0.0001$. Test accuracy of RWM; ITI and RTI was: 75%; 88% & 94% respectively for LAD disease; 44%; 75% & 75% for LCX, and finally 75%; 81% & 63% respectively for RCA disease.

MCE settings on ATL HDI 5000 system

Imaging mode	Intermittent Triggering (PI)	Real-Time (PI)/Doppler (PPI)
Scanhead & Preset	P4-2, CSI	P4-2, CSI
Mechanical Index (MI)	0.53 - 0.8 MHz	0.16 - 0.22 MHz
PRF, Scan Line Density	2500, A	2500, A
Persistence/Dynamic Range	Low/Low	Low/Low
Sensitivity/Frame Rate	Medium/Medium	Medium/Medium
Color Gain	–	55-65% (PPI only)
Potentiometers	Max TGC but for top 2	Max TGC but for top 2
Focus	10 - 13 cm	10 - 13 cm

PI= Grayscale Pulse Inversion, PPI= Power Doppler Pulse Inversion

Conclusion: MCE in either ITI or RTI is of added value to RWM, in DSE; especially for LAD disease diagnosis.

P1625 Contrast echocardiography is superior to single photon emission computed tomography for detection of functional significant coronary stenosis

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Objective: Comparison of myocardial contrast echocardiography (MCE) and single photon emission computed tomography (SPECT) during vasodilator stress for the detection of functional significant coronary heart disease in patients (pts) without previous myocardial infarction. Methods: 21 consecutive pts (mean age 60±9 years) were studied with simultaneous myocardial contrast echocardiography (MCE) using a continuous intravenous infusion of Sonazoid® (NC100100) and SPECT (99mTc) after standard dipyridamole stress (0.852 mg/kg over 6 minutes). Regional function (RF) was assessed at rest and stress in real time. MCE was performed using intermittent pulse inversion imaging (ATL 5000) with increasing trigger intervals. Measurement of myocardial fractional flow reserve (FFR) with a cut-off value of 0.75 obtained during coronary angiography was used as reference method to assess the functional severity of coronary artery stenosis. All images from the MCE studies were stored digitally and assessed visually independent from wall motion by a blinded observer.
Results: 16 pts showed functional significant stenosis according to the FFR measurements (mean FFR 0.54±0.10, 10 LAD-, 4 CX- and 2 RCA-territory) and 5 patients showed less severe stenosis (mean FFR = 0.86±0.09, 3 LAD, 1 CX and 1 RCA territory). On a per patient analysis, the sensitivity to detect functional significant coronary heart disease of MCE and SPECT were 94% and 63% respectively, while RF became abnormal only in 32% of patients ($p<0.001$ vs MCE and 0.156 vs SPECT). Specificity was 80% for MCE and RF and 100% for SPECT.
Conclusion: In pts without previous myocardial infarction MCE using intermittent pulse inversion imaging is superior to SPECT for the detection of functional significant coronary heart disease. Both perfusion methods were better than RF assessment in this regard.

P1626 Accuracy of adenosine contrast echocardiography is higher in patients with single-vessel than multi-vessel coronary artery disease

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Background: We have previously shown that myocardial perfusion is accurately assessed by adenosine contrast echocardiography (ACE) following PESDA infusion in pts with coronary artery disease (CAD). The aim was to compare this accuracy in single-vessel (SV) versus multi-vessel (MV) pts with angiographic diagnosis of coronary artery disease (CAD).
Methods: ACE with PESDA was performed in 74 pts with SV CAD (57 male, 61±11 years) and 57 with MV CAD (44 male, 62±12 years). ACE with PESDA was visually assessed, at rest and after IV bolus injection of 6-18 mg of adenosine (ADN) using triggered (1:1) 2nd harmonic imaging. Normal perfusion was defined as a marked increase in the wall contrast enhancement after ADN and abnormal perfusion was the abscense of this enhancement after ADN. Angiography was done not later than 30 days from ACE. For each pt 3 LV territories (LAD, RCA and CX arteries) were considered (171 segments in the MV group and 222 in the SV). Sensitivity (Sens), specificity (Spec), accuracy (Accur), positive (PPV) and negative (NPV) predictive values were calculated.
Results: Gender (p=0.851) and age (p=0.619) were similar for both groups. Table shows the comparison between groups.

	Sens	Spec	PPV	NPV	Accur
SV n=74 pts	95.9% (71/74)	99.3% (147/148)	98.6% (71/72)	98% (147/150)	98.2% (218/222)
MV n=57 pts	89.6% (121/135)	100% (36/36)	100% (121/121)	72% (36/50)	91.8% (157/171)
p	0.185	0.460	0.785	0.0001	0.006

Conclusion: ACE is a reliable method to detect CAD with higher NPV and accuracy in SV CAD patients.

P1627 Detection of myocardial viability using dobutamine stress echocardiography and myocardial contrast after acute myocardial infarction

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Background: The discovery of a microbubble based echocardiographic contrast agent emerged the potential of improvement in the diagnostic accuracy of stress echocardiography.
Objective: We evaluated the diagnostic value of dobutamine stress echocardiography (DSE) and myocardial contrast echocardiography (MCE) using second harmonic with and without intermittent imaging in the detection of myocardial viability after acute myocardial infarction (AMI) treated with successful thrombolysis.
Methods: We studied 50 patients (pts) in the first week after AMI, at rest with low dose DSE, with and without MCE. We evaluated the recovery of left ventricular ejection fraction (LVEF) at rest by two-dimensional echocardiography as well as by myocardial scintigraphy (Mibi Spect), between the fourth and sixth month of follow-up. According to a absolute 5% increase in LVEF measured by the two Mibi Spect studies, pts were divided in group I, with functional recovery (19 pts) and group II, without functional recovery (31 pts). To analyze the contractility and myocardial perfusion, a left ventricular wall motion score index (WMSI) and myocardial perfusion score (MPSI) index at rest and after dobutamine were created.
Results: When using the evaluation of contractility by DSE in order to predict the LVEF recovery, sensitivity was 95%, specificity 87%, positive predictive value 82%, negative predictive value 96% and diagnostic accuracy 90% (kappa= 0.794). When we analyzed the diagnostic accuracy of MCE, we demonstrated sensitivity of 95%, specificity of 52%, positive predictive value of 54%, negative predictive value of 94% and diagnostic accuracy of 68% (kappa= 0.479).
Conclusion: The detection of contractile reserve by the use of DSE was sensitive and specific in predicting LVEF in pts after AMI treated with successful thrombolytic therapy, while MCE demonstrated high negative predictive value.

P1628 Cyclic variation of backscatter myocardial signal in type I diabetes and in hypertension: an ultrasonic tissue characterization study

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Early changes detected in myocardial ultrastructure of diabetic and hypertensive heart consist of increased interstitial collagen deposition, although with different physiopathologic patterns. Aim of this study was to characterize both myocardial echodensity and its cyclic variation in type 1- diabetes, compared with essential hypertensive patients, both with normal conventional 2D echo findings, and to determine whether ultrasound tissue characterization can detect ultrastructural changes of myocardium, as an increase in collagen content. We evaluated 10 type-I-diabetic pts (D), 10 essential hypertensive pts (H), both with normal regional and global resting function and 10 age- and sex-matched controls (C). All D were affected by diabetic nephropathy with renal failure and mild degree of hypertension. By selection, all D and H pts. had a negative maximal exercise stress test, to avoid confounding effects of coronary artery disease. All study subjects performed: conventional 2D-Doppler echocardiography; ultrasonic myocardial integrated backscatter (IBS) trough Acoustic Densitometry package (Philips Sonos 5500). We considered: absolute diastolic IBS value both at interventricular septum and at posterior level, indexed (%) by pericardial IBS value, to optimise the comparison between subjects, (expression of echodensity) and systo-diastolic variation of the backscatter (Cyclic Variation Index (CVIibs), as index of intrinsic myocardial contractility. Left ventricular mass was significantly higher in hypertensive, although within normal range (H: 119±4 vs D: 113±24 and C: 96±12; $p<.01$). Systolic function overlapped in three groups. Diastolic function obtained trough the E/A ratio of mitral flow velocity pattern showed slightly but significant difference of both groups with controls (H: 1.10±0.2 vs. D:1.18±0.3 vs C: 1.6±0.3; $p<0.001$). Echodensity at interventricular septum level was significantly higher in diabetic patients in comparison both with hypertensive and controls (D: 68 ±3 vs H 51.3 ±11 and C: 50.6±12.8; $p< 0.005$). CVIibs at interventricular septum level was significantly lower both in hypertensive an diabetics in whom overlapped, in comparison with controls (D: 10.7±9.6 vs H:12.7±9.9 and C: 24.6 ±4.5; $p<0.001$). The coexistence of diabetes (plus renal failure) and hypertension is able to induce a further increase in collagen deposition at myocardial level, thus altering the intrinsic contractility. This physiopathologic worsening could prelude to develope a preclinical or overt overall left ventricular dysfunction.

P1629 Detection of early myocardial changes in diabetic heart disease

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Background: Diabetes is associated with increased interstitial collagen deposition. We sought whether early changes in myocardial contractility could be identified with tissue characterization, and to compare pts with diabetes with and without LV hypertrophy, to determine whether these changes in the diabetic heart are independent of LV hypertrophy.
Methods: We studied 179 pts with normal ejection fraction and no evidence of coronary disease based on symptoms, ECG and stress echo; 48 with diabetes only (DM group), 45 with both diabetes and LVH (DH group), 44 with LVH only (LVH group), and 42 normal controls (CON group). Cyclic variation (CV) of integrated backscatter (IB) of 16 segments and strain and strain rate of 6 walls in apical four, long axis and two chamber views were evaluated and averaged for each patient. Calibrated IB was assessed by comparison of the septal or posterior wall with pericardial IB intensity in parasternal long axis view.
Results: Three patient groups (DM, DH, LVH vs CON) showed significant decreases in CV, end-systolic strain, peak strain, strain rate and increases in calibrated IB in both the septum and posterior wall compared with controls. There were no significant differences found in CV among DM, DH and LVH groups and end-systolic strain, peak strain and strain rate between DM and LVH groups, but significant differences were found between DM and DH groups and between LVH and DH groups in end-systolic strain ($p < 0.01, 0.05$), peak strain ($p < 0.05, 0.01$) and strain rate ($p<0.01, 0.01$). Only significant difference was found between DM and DH groups in posterior calibrated IB.

CV and strain parameters

	DM	DH	LVH	CON
CV	6.39 + 1.36	6.24 + 1.03	6.66 + 1.15	7.59 + 1.35
End-systolic strain	22.29 + 2.67	20.68 + 2.70	21.90 + 2.87	24.70 + 3.54
Peak strain	23.37 + 3.02	22.05 + 2.87	23.97 + 3.04	26.31 + 3.67
Calibrated IB	-18.64 + 7.89	-17.13 + 7.02	-17.47 + 6.41	-22.0 + 6.76

Conclusions: Cyclic variation, strain and strain rate are decreased and calibrated IB is increased in diabetic patients without overt heart disease. Although similar to changes caused by LVH, these changes are independent of LVH and do not appear to be additive. These findings diabetes may independently be associated with reduced myocardial contractility.

P1630 Ultrasonic integrated backscatter of the myocardium in anorexia nervosa

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Background: Cardiac involvement is an important feature of anorexia nervosa. A reduced left ventricular mass with preserved myocardial contractile function has been previously reported. The aim of the present study was to evaluate the cyclic variation of integrated backscatter (IBS-CV) of the myocardium in patients with anorexia nervosa and whether the examination of cardiac acoustic reflectivity plays a role to detecting initial stage of myocardial abnormality in these patients.
Methods: Twenty-five female (aged 21.3±3.7 years) with anorexia nervosa, compared with 25 age-matched thin and 25 age-matched controls with BMI >20 Kg/m^2, underwent either conventional 2-dimensional echocardiogram or analysis of IBS-CV.
Results: Anorexic patients, compared with thin and control women, showed reduced left ventricular mass (LVM: 82.9±17.1 vs 119.9±13.8 and vs 126.12±16.4 g, $p<0.0001$; LVM indexed 21.4±3.3 vs 29.4±2.5 and vs 31.2±3.1 g/m^2.7, $p<0.0001$), and IBS-CV (septum: -0.49±2.18 vs 6.86±1.3 and vs 6.61±1.74 db, $p<0.0001$; posterior wall: 2.77±2.12 vs 7.15±2.12 and vs 7.48±2.23 db, $p<0.01$). Moreover, IBS-CV is related to LVM, as absolute ($r=0.55$, $p<0.05$; $r=0.48$, $p<0.05$) and indexed ($r=0.70$, $p<0.005$; $r=0.58$, $p<0.05$) values.
Conclusion: The present study confirms a reduced LVM in the starvation phase of anorexia nervosa and demonstrates a significant reduction of the IBS-CV at septum and posterior wall levels, which is also related to left ventricular hypotrophy. Since these abnormalities in ultrasonic properties has been substantially related to variations of the intramural contractile performance, our findings could represent a pre-clinic index of myocardial dysfunction in patients with anorexia nervosa.

P1631 Cyclic variation of the myocardial integrated backscatter signal in essential hypertensive patients with microalbuminuria

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Microalbuminuria (MA) is a well-recognized marker of cardiovascular complications in hypertension. Since acoustic properties of the myocardium are sensitive to the myocardial structure and the contractile conditions of myocyte, we evaluated cardiac dysfunction based on the integrated ultrasonic backscatter. The aim of study was to analyze the cyclic variation of integrated backscatter (CVIBS) in 2 groups of hypertensive patients with microalbumiuria or not.
Method: A group of 28 essential hypertensive patients (mean age 51±8) who had controlled blood pressure (mean 24-h BP <140 and/or < 90 mm Hg) were analyzed with a group of age comparable normotensive subjects as controls (n=20). MA was found in 10 patients, classified as MA+ (urinary albumin excretion (UAE) 20 to 300 mg/24 h); 18 patients had normal UAE (< 30 mg/24 h) and were classified as MA-. Microalbuminuria was evaluated as mean value of 24-h UAE from 24-h urine collection. Diabetes mellitus and major noncardiovascular diseases were the exclusion criteria. The parasternal short-axis view at the papillary muscle level was used to obtain the 2-D image of integrated backscatter. For each patient, three regions of interest were chosen in the same parasternal short-axis image (Midanteroseptal, midposterolateral, midinferior areas). We determined the magnitude of CVIBS in decibels as the difference between the maximal and minimal values in a cardiac cycle.
Results: The MA (+) and MA (-) groups did not differ with regard to age, sex, body mass index and left ventricular hypertrophy. The left ventricular mass index values between control group and hypertensive patients were significantly different ($p<0.05$). The three regions of myocardial CVIBS values of MA+ group were significantly lower than MA- hypertensive group and control group ($p<0.05$).

	MA +(1)	MA -(2)	Control(3)	P(1-2)	P(1-3)	P(2-3)
CVIBS AS	5.4±1.5	7.4±1.3	7.5±1.2	*	*	NS
CVIBS PS	6.1±1.4	7.8±1.2	7.6±1.3	*	*	NS
CVIBS MI	6.1±1.6	7.4±1.2	7.3±1.1	*	*	NS

CVIBS:Cyclic variation of integrated backscatterAS: anteroseptal PS: posteroseptalMI: midinferiorNS: Non-significant*: $p<0.05$

Conclusion: These data suggest that myocardial integrated backscatter of hipertensive microalbuminuric patients may help define the presence and extent of myocardial structural abnormalities.

P1632 Accuracy of stress-induced reduction of subendocardial backscatter variations in CAD patients with or without EKG signs of myocardial ischaemia

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Background: During peak stress test, myocardial ischemia occurs earlier in the subendocardium (ENDO) than in the subepicardium (EPI), impairs at first myocardial contractility and only later surface EKG. Since integrated backscatter cyclic variations (IBCV) are reduced during ischemia, we hypothesized a reduction of ENDO IBCV earlier than EKG signs of ischemia.
Methods: We analyzed 78 myocardial segments supplied by a coronary artery with >50% stenosis (CAD) in 37 patients and 27 segments in a control group of 12 patients with no-CAD. In each patient a transgastric two-chamber view was acquired during an atrial pacing stress test. IBCV were calculated in ENDO and EPI at rest, and during peak (150 b/m') atrial pacing (stress) and immediately after pacing interruption.
Results In the control group of no-CAD segments both ENDO and epi IBCV remained unchanged in all the steps of pacing stress test. At peak stress, 12 of the CAD patients, with 25 myocardial segments, showed ST EKG-changes significant for myocardial ischemia (ISCH) and 25 of the CAD patients with 53 segments did not show ischemia (NO-ISCH). In both NO-ISCH and ISCH segments the ENDO IBCV decreased from rest (7.9±2.3 and 8.2±2.3) to stress (5.5±2.1 and 5.3±1.3, $p<0.0001$ vs rest), and recovered immediately after pacing interruption (7.7±2.9, and 7.3±3.4 $p<0.0001$ vs peak); the EPI IBCV did not change along the protocol.

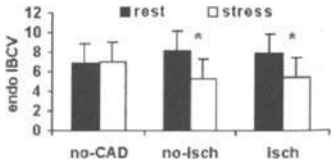

Figure: IBScv subendo at rest and stress.

Conclusion: ENDO IBCV are accurate in detecting subendocardial ischemia in CAD patients with or without ST EKG-changes.

P1633 Ultrasonic tissue characterization (backscatter) in the analysis of left ventricular myocardial intrinsic function in systemic amyloidosis

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Amyloidosis is a systemic illness characterized by the deposition in the extracellular compartment of protein fibrillar autholog material (amyloid), that determines organ damage. Aim of study is to evaluate if ultrasonic tissue characterization can allow a precocious detection of amyloidosic cardiac involvement. We have studied 15 patients with sistemic amyloidosis (GROUP A) (positive ness of the biopsy of the subcutaneous fat to red Congo), and an age-sex-matched healthy group(GROUP B). All subjects performed a conventional color Doppler echocardiography (Philips, Sonos 5500),for evaluation of left ventricle systolic and diastolic function. Acoustic Densitometry was applied for analysis of backscatter (IBS) sampled in a R.O.I. placed at septum level and posterior wall, both at end-diastole (IBSd) and end -systole (IBSs). The pericardial backscatter value in dB was placed equal to 100 towards the diastolic level of the values IBS of the septum and the posterior wall. Cyclic variation of the signal in backscatter both to posterior wall and septum (CVI = IBSd-IBSs/IBSd*100) was also calculated, as an index of intrinsic contractility of the myocardium.

Left ventricular mass was higher in the group A. (A.: 157.3± 39.9, B: 101.5 ±12.9 g/m^2, $p < 0.0001$) and particularly for diastolic thickness of the septum (A.: 1.29 ± 0.27, B: 0.98± 0.08 cm, $p < 0.001$) and of posterior wall (A.: 1.10± 0.19, B: 0.92 ± 0.08 cm, $p < 0.002$), that resulted significantly higher in the group A. Left ventricular systolic function (fractional shortening) was comparable in the two groups. The E/A relationship of the diastolic transmitral flow in the amyloidosic subjects, was significantly lower in comparison with control group (A.: 0.95± 0.3, B: 1.5 ± 0.33, $p < 0.01$). The CVI at septum level (A.: 17.3% ±s 12.5, B: 40.5%± 12.9, $p < 0.0001$) and at posterior wall level(A.: 20.4% ±s 18.5, B: 44.5%± 14.9, $p < 0.001$) were significantly lower in the amyloidosic group. The percentage of the IBSd in comparison to the pericardium, both for the septum and for posterior wall was significantly higher in Group A. The reduction of the CVI in the group A, could be the expression of a precocious alteration of the intrinsic myocardial contractility, also when the normal indexes of left ventricular systolic function are still normal. Therefore, the ultrasonic tissue characterization could be useful in the precocious detection of alterations of the myocardial " texture" in sistemic amyloidosis, which could be in relationship to deposit of amyloid at myocardial level.

COMPARATIVE MYOCARDIAL IMAGING

P1634 Assessment of segmental wall motion using real-time magnetic resonance imaging: comparison with 2D echocardiography and breath-hold true FISP

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Non-triggered, non-breath-hold real-time cardiac MRI may be a valuable alternative to echocardiography for the assessment of regional wall motion in patients with poor acoustic window. We compared standard 2D echocardiography with second harmonic imaging (ECHO) to two different interactive real-time MRI techniques using 1) a spiral gradient echo sequence (SPIRAL; TE/TR 4/30 ms, 3 interleaves, matrix 128x256) and 2) a radial true FISP sequence (RADIAL, TE/TR 1.3/2.9 ms, 80 radials, matrix 128x128). An ECG-triggered, breathhold trueFISP sequence (BH-TF, TE/TR 1.8/3.6ms, matrix 128x256) was used as reference standard for wall motion assessment. MRI was performed on a 1.5 T scanner (ACS-NT, Philips, Best, The Netherlands). An interactive user interface allowed on-the-fly free plane definition during real-time scanning. With all modalities standard views including a mid-ventricular short-axis view and 3 long-axis views were acquired. Segmental endocardial visibility (0=poor to 2=good) and regional wall motion (0=not evaluable to 4 dyskinesia) were scored according to the 16 segment model of the ASE for all techniques. 33 non-selected patients referred for routine echocardiography were included.

Results: Nine patients had atrial fibrillation. Out of matched 528 segments acquired with all four modalities poor visibility was present in 18.6% of segments with ECHO, 14.5% with SPIRAL (ns vs. ECHO), 1.4% with RADIAL ($p<0.001$ vs. ECHO and SPIRAL) and 0.4% with BH-TF (ns vs. RADIAL). For the short-axis view the percentage of segments with good image quality was *not* different between the three MRI approaches but was significantly larger compared to ECHO ($p<0.001$). However, for the long-axis views the percentage of segments with good image quality was least for SPIRAL ($p<0.05$ compared to ECHO) and largest for RADIAL and BH-TF ($p<0.001$ vs. ECHO; p=ns vs. RADIAL). There was a tendency for a higher mean wall motion score for ECHO compared to BH-TF (p=0.06). Agreement on the scoring of regional wall motion relative to BH-TF increased form ECHO (Kappa 0.71) to SPIRAL (Kappa 0.84) to RADIAL (Kappa 0.92).

Conclusion: Interactive real-time MRI using RADIAL is of similar quality to standard BH-TF and superior to ECHO and SPIRAL for the visualization of segmental wall motion in this group of unselected patients. RADIAL may complement echocardiography for the assessment of regional function in patients with a limited acoustic window.

P1635 Quantitative myocardial perfusion imaging in a combined PET-CT scanner: CT- versus germanium-transmission using different reconstruction algorithms

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Background: In routine PET-scanning a 20 minute transmission scan for attenuation correction with a rotating 68 Germanium (Ge) source - reconstructed iteratively (IT) or with filtered backprojection (FBP) - is commonly used. This is a time-consuming procedure which could be considerably shortened by use of a rapid CT-scan for attenuation correction.

Aim: To evaluate the influence of reconstruction parameters on absolute values of myocardial blood flow (MBF) using conventional transmission scans vs. CT scans for attenuation correction in a combined PET-CT scanner (GEMS, Milwaukee, USA).

Methods: 13N-labelled NH3 and PET was used to measure MBF (ml/min/g) at rest in 4 patients with documented coronary artery disease. Emission was preceeded and followed by three CT scans (140 kV, 10 mA, scan length 15cm, rotation time 0.5 sec., total scan time 3.7 sec.) and one Ge transmission. Emission was then reconstructed using CT (n=24) vs. Ge (n=8) for attenuation correction, both with IT and FBP.

Results: Values for MBF (given in ml/min/g) at rest were: Ge(FBP) 0.75 ± 0.14, Ge(IT) 0.76 ± 0.21 (p=ns); CT(FBP) 0.80 ± 0.10, CT(IT) 0.74 ± 0.20 ($p<0.05$). The reproducibility coefficient for comparison of each measurement to conventionally corrected PET is given below according to Bland and Altmann (1.96 x SD of mean difference).

Conclusions: Use of CT attenuation correction is feasible and provides results which are highly comparable to those achieved by Ge attenuation correction. However, use of the same reconstruction algorithm is crucial.

P1636 The correlation between myocardial absolute uptake of ^{99m}Tc-MIBI and pressure-derived myocardial fractional flow reserve in the LAD versus RCA

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The development of coronary pressurewire facilitates the measurement of fractional flow reserve (FFR) to assess the functional severity of coronary-artery stenoses. To evaluate the correlations between FFR and myocardial absolute uptake of 99mTc-MIBI in LAD versus RCA, 34 patients underwent 99mTc-MIBI SPECT with two-day protocol using 740MBq of 99mTc-MIBI each day. Quantitative analysis with the measurement of percent uptake and absolute count of 99mTc-MIBI was performed. In all patients, exercise-induced increase in 99mTc-MIBI percent uptake and absolute count correlated with FFR ($r=0.42$, $p<0.02$ and $r=0.38$, $p<0.03$, respectively). In 22 patients in whom LAD was evaluated, the best correlation of $r=0.58$ ($p<0.005$) was found between exercise-induced increase in 99mTc-MIBI absolute count and FFR, followed by the correlation ($r=0.50$, $p<0.02$) obtained with exercise-induced increase in 99mTc-MIBI percent uptake. In the remaining 12 patients in whom RCA was evaluated, no significant correlation was observed between exercise-induced 99mTc-MIBI increase either with relative or absolute count measurements. These results suggest that noninvasive assessment of coronary physiology may be limited in RCA, due partly to the influence of RI count of extracardiac organs such as the liver. In LAD, however, 99mTc-MIBI scintigraphy using quantitative analysis enables the noninvasive assessment of the magnitude of functional significance of coronary artery stenosis, which is far more important than the conventional evaluation of the coronary lumen.

P1637 Comparison of dobutamine echocardiography and dual SPECT (^{201}Tl and ^{123}I-BMIPP) for prediction of functional recovery after acute myocardial infarction

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Purpose: Discordance between I-123 BMIPP and Tl-201 SPECT is an effective method to assess myocardial viability (MV). This study was performed to compare low dose dobutamine echocardiography (LDDE) and dual SPECT for assessment of MV and prediction of functional recovery after acute myocardial infarction (AMI).
Methods: LDDE and dual SPECT were studied in 35 pts 7 to 14 days after AMI, of which 28 pts underwent coronary revascularization at the acute stage. Assessment of dual SPECT was performed by comparing defect score of I-123 BMIPP and Tl-201, and MV was considered positive when difference of the defect score was significant. Left ventricular wall motion score (WMS) was estimated, and MV was considered positive when WMS decreased during LDDE. Echocardiography was performed 6 month later to assess functional recovery of the dysfunctional myocardium.
Results: The rate of agreement of MV between dual SPECT and LDDE in early stage of MI was 77% ($P<0.01$). In 22 pts with positive MV by SPECT, LDDE showed MV in 16 (positive predictive value = 73%). In 13 pts with negative MV by SPECT, 11 showed negative MV by LDDE (negative predictive value = 85%). The long -term functional recovery was observed in 20 of 33 pts (60%). The positive and negative predictive values for functional recovery by dual SPECT were 73% (16/22) and 64% (7/11), respectively ($p<0.05$). The positive and negative predictive values for functional recovery by LDDE were 100% (18/18) and 87%(13/15), respectively ($p=0.00001$). Five of 6 pts with positive MV by dual SPECT without functional recovery had residual stenosis at the infarct-related arteries.
SPECT score was compared in pts with and without functional recovery. Both 201-TlCl and 123I-BMIPP scores were significantly smaller in pts with functional recovery ($p<0.01$), but the difference of the two scores was greater in pts with functional recovery ($p<0.01$).
Conclusion: Assessment of MV using LDDE is concordant with those by dual SPECT in the early stage of AMI. LDDE had a higher predictive value for long - term functional recovery at the infarct area in comparison with dual SPECT. However, positive MV by dual SPECT without functional recovery may reflect residual stenosis at the infarct-related arteries. Thus, combining assessment of dual SPECT and LDDE is an useful method to detect myocardial viability and residual stenosis at the infarct-related vessels and to predict long-term functional recovery. In addition, the study suggested that the extent of myocardial viability was greater in pts with smaller size of infarct or risk area.

P1638 Contrast-enhanced MRI for the assessment of myocardial viability: comparison with ^{18}F-fluorodeoxyglucose-positron emission tomography

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Contrast-enhanced (CE) MRI has been shown to predict recovery of function after revascularization in patients with chronic coronary artery disease. The value of the technique in comparison to the in-vivo gold standard for viability assessment, 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET), is not fully established. We compared CE-MRI to FDG-PET in 23 patients with chronic ischemic heart disease and left ventricular dysfunction referred for myocardial viability assessment. For CE-MRI an inversion-recovery gradient-echo sequence (TE/TR 4.4/9.6 ms, FA 25°, typical TI 250-300 ms, resolution 1.3x1.6x5mm) was used on a 1.5T MR scanner (Magnetom Sonata, Siemens, Erlangen, Germany) 20 minutes after administration of 0.2 mmol/kg Gadolinium-DTPA. Data acquisition was performed in short-axis views covering the whole left ventricle and in selected long-axis views. FDG-PET was performed under hyperinsulinemic euglycemic clamp (ECAT EXACT HR+, Siemens, CTI). Resting perfusion was assessed using SPECT. For data analysis we used a 17-segment model including 6 basal, 6 midventricular, 4 distal segments and the apex. According to PET/SPECT findings segments were categorized as either viable or non-viable. Results of quantitative FDG-PET analysis were compared to the segmental extent of hyperenhancement (SEH) at CE-MRI in corresponding segments.
Results: Mean ejection fraction was 31±11%. A total of 391 segments were analyzed with both techniques. Viable segments by FDG-PET showed significantly less SEH compared to non-viable segments (8.5±16.3% vs. 80.2±23.1%; $p<0.001$). The segmental glucose uptake at PET was inversely related to the SEH ($r=-0.78$; $p<0.001$). By ROC analysis the area under the curve was 0.97. Using a cutoff value of 37% given by the ROC curve the accuracy for identification of myocardial viability was 94% in all segments and 88% in akinetic segments with a high level of agreement (Kappa 0.77).
Conclusion: CE-MRI has comparable diagnostic accuracy as PET for the evaluation of myocardial viability in patients with chronic ischemic heart disease and left ventricular dysfunction.

P1639 Magnetic resonance angiography versus conventional coronary angiography to diagnose coronary artery disease

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Magnetic resonance angiography (MRA) has recently emerged as an alternative to the "gold standard" of conventional coronary angiography (CA) for the diagnosis of coronary artery disease. Sensitivity and specificity of MRA still need to be established. Methods: Thirty-three consecutive pts (23 m; 60 ± 11 years) with suspected, or suspected progressive, coronary artery disease underwent MRA prior to CA. MRA and CA findings were evaluated independently by a radiologist and a cardiologist, respectively. Only stenoses > 50% by visual assessment were entered into the analysis. Results: On CA, 14 pts had no lesions, whereas the other 19 pts had a median of 1 (range 1-4) lesion, for a total of 32 lesions. There were 7 lesions in the left anterior descending coronary artery (LAD), including 3 in the first diagonal branch, 11 in the left circumflex coronary artery (LCx), including 4 in the obtuse marginal branch, 13 in the right coronary artery (RCA), and 1 in the left main coronary artery. The former 3 arteries were divided into proximal, medial and distal segments. Sensitivity and specificity of MRA (with CA findings serving as reference) in diagnosing LAD lesions were 57.1 and 61.5%, respectively, with 30.3% false positive (FP) and 9.1% false negative (FN) findings. Corresponding values for the LCx were 63.6 and 63.6%, respectively (FP 24.2%, FN 12.1%), and for the RCA 84.6% and 95.0%, respectively (FP 3.0%, FN 6.1%). When sidebranches and distal vessel segments were excluded from the analysis, MRA sensitivity and specificity improved to 80.0 and 75.0% (LAD), 100 and 74.1% (LCx), and 91.7 and 95.2% (RCA), respectively. Of the 33 pts, only 1 pt (3%) who had a 90% stenosis of the medial RCA on CA was diagnosed by MRA as having no lesions. Conclusion: MRA has a high sensitivity and specificity in diagnosing proximal and medial coronary artery lesions. The diagnostic accuracy of the technique needs to be improved for distal lesions and sidebranches before MRA can supplant CA.

P1640 NOGA electromechanical mapping versus PET in prediction of post-revascularization myocardial function in patients with severe heart failure

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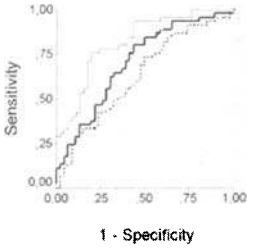
We compared catheter-based electromechanical mapping (NOGA®) with PET for prediction of reversibly (RDM) and irreversibly dysfunctional myocardium (IDM) in pts with ischemic cardiomyopathy. Furthermore, we identified the optimum discriminatory value of NOGA measurements for distinction between RDM and IDM.
Methods: 20 pts (19 males, age (mean±SD) 60±16 years, EF 29±6%) underwent viability testing with NOGA and PET prior to CABG (N=11) or PTCA (N=9). MRI and 3-D echocardiography was performed at baseline and 6 months after revascularization (9 segment model) to identify RDM and IDM regions.
Results: EF increased to 34±13% 6 months after revascularization ($P<0.05$ vs baseline). The correlation between regional myocardial PET tracer uptake and NOGA unipolar voltage amplitude (UVA) was modest ($r=0.29$, $P<0.01$). The 58 RDM and 57 IDM regions differed with regard to UVA (9.2±3.9 mV vs 7.6±4.0 mV, $P<0.05$), normalized UVA (106±54% vs 75±39%, $P<0.05$), and tracer uptake (76±17% vs 60±20%, $P<0.05$). NOGA local shortening did not distinguish between RDM and IDM (6.4±5.8% vs 5.4±6.6%). By ROC-curve analysis (figure) PET tracer uptake had better diagnostic performance than UVA (area±SE: 0.82±0.04 vs 0.63±0.05, $P<0.05$) and normalized UVA (area 0.70±0.04, $P<0.05$ vs tracer uptake). Optimum threshold was defined as the value yielding sensitivity = specificity for prediction of RDM. Sensitivity and specificity was 59% at a UVA of 8.4 mV, 65% at a normalized UVA of 83%, and 78% at a tracer uptake of 69%.



ROC-curve analysis. Upper curve: PET tracer uptake; Middle curve: NOGA normalized UVA; Lower curve: NOGA UVA.

Conclusions: NOGA can discriminate between RDM and IDM using UVA. However, the diagnostic characteristics of PET are superior to NOGA in pts with severe heart failure. Optimum discriminatory values for absolute and normalized UVA are 8.4 mV and 83%, respectively.

P1641 Blood oxygen level dependent (BOLD) MRI for the detection of scarred and viable myocardium, a PET comparative study

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The identification of impaired but viable myocardium in patients with coronary heart disease is of crucial clinical importance since it is likely to benefit from revascularisation. Positron Emission Tomography (PET) is the gold standard in detecting viable myocardium. However, it is expensive and not widely available.
Aim: to investigate the use of a new modality of magnetic resonance imaging (MRI), Blood Oxygen Level Dependent (BOLD) that relies on changes in deoxyhaemoglobin level under stress, in the detection of scarred and viable myocardium in comparison to PET images.
Method: nineteen patients with established coronary artery disease and impaired left ventricular contraction and at least one area of akinesis, underwent a rest and dipyridamole stress MRI, using a double breath hold T2* weighted, ECG gated sequence to produce BOLD contrast images. A dynamic 13N-ammonia (13NH3) and ECG gated 18F-fluorodeoxyglucose (FDG) PET scans followed the MRI. The signal change on BOLD MRI and Wall thickening were compared between rest and stress images in the viable and scarred segments, identified on PET scans. Scarred myocardium is defined by the matched decrease in perfusion and metabolism, while the presence of perfusion-metabolism mismatch defects defines impaired but viable myocardium.
Results: Two short axis slices of mid ventricle, with 8 segments each, were analysed giving a total of 304 segments. The slices were matched anatomically between MRI and PET. Using PET, 68 segments were identified as viable and 42 segments as scarred tissue. The viable segments were found on MRI to have an average signal change of –9.53 between rest and stress, while the average signal change in the scarred segments was –2.15 (P=0.008). The average wall thickness in the viable segments was 8.7 mm compared to 5.9 mm in the scarred segments (P<0.0001).
Conclusion: BOLD MRI with measurement of wall thickness may be used for detection of scarred and viable myocardium and help in identifying suitable patients for revascularisation. Further larger studies are needed to establish sensitivity and specificity.

P1642 Quantification of viable rim thickness by contrast-enhanced magnetic resonance of dysfunctional myocardium and its relation to metabolic state

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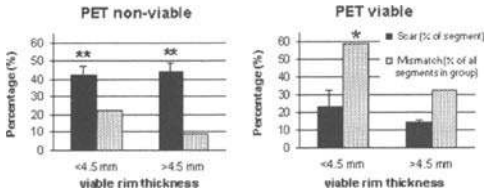
Background: Metabolic assessment of dysfunctional myocardium by PET allows prediction of recovery of contractile function following revascularization. Contrast-enhanced MR was used to determine the transmural distribution of viable tissue and scar in PET-viable and non-viable myocardium.
Methods and results: Seventeen patients with old myocardial infarctions were studied with MR and PET. In 56-64 segments/heart mass and thickness of viable tissue on MR (0.25mmol/kg of GD-DTPA-BMA, inversion recovery technique) was compared with 18F-fluorodeoxy-glucose (FDG)-uptake of corresponding segments. Mass of viable tissue and FDG-uptake (both normalized to the segment with highest resting flow on 13N-ammonia-PET) correlated (p<0.0001) with both, segments with balanced flow-metabolism (ratio <1.4; r=0.82) and slightly worse with mismatch segments (r=0.62). A ROC analysis yielded a sensitivity/specificity of 91%/86% (AUC 0.94) for MR to detect viable myocardium (≥50% FDG-uptake). Rim thickness correlated with FDG-uptake (r=0.80). FDG-uptake of ≥50% predictive for functional recovery coincided with a rim of 4.5mm. 82% of all dysfunctional segments were viable on PET, in 96% of these segments viable rim was ≥4.5mm and scar was low 14±1% (mean±SEM, figure, **p<0.001 vs PET-non-viable). In the remaining 4% with a small rim (<4.5mm) the portion of mismatch segments was highest (59%, figure, *overall-p<0.005). In 47% of PET-nonviable segments a viable rim ≥4.5mm was found with a scar mass as high as in segments classified non-viable by both techniques.



Conclusions: Contrast-enhanced MR detects viable tissue with high sensitivity and specificity. Combining MR and PET findings identifies different subsets of myocardial segments which may improve prediction of functional recovery.

PERCUTANEOUS CORONARY INTERVENTION OUTCOMES

P1643 Long-term outcome of stenting of bifurcation lesions, based on side branch size and stenosis

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Background: Percutaneous Coronary intervention (PCI) of bifurcation lesions pose increased risk of complications. The impact of side branch size and stenosis on the long term outcome of PCI of these lesions is not well known.
Methods: We retrospectively analyzed 700 consecutive angioplasty films and identified 71 patients (10.1%) with bifurcation lesions meeting study criteria. All patients had successful main vessel PCI & stenting with or without side branch PCI. Patients were divided into 3 study groups based on side branch PCI: Group I had successful side branch rescue PCI, Group II had acute side branch occlusion and failed rescue PCI, Group III had small side branch, which did not warrant PCI, but had post procedural side branch residual stenosis of > or equal to 70%. Each patient received standard doses of I.V heparin, Gp II b/IIIa inhibitors and clopidogrel.
Results: Refer to the table below for results. Severely stenosed large side branch (Grp II) are more likely to close during PCI and have worse clinical outcome. Patients with successful rescue PCI of large side branch (Grp I) as well as patients without rescue PCI of smaller side branch (Grp III) have good short and long term outcome.
Conclusions: Aggressive strategies to preserve large side branches result in much better clinical outcome.

Abstract P 1643 – Table: Outcome of Bifurcation Lesions

Groups	Size of the side branch	Pre PCI stenosis (side branch)	Post PCI stenosis (side branch)	Residual side branch stenosis	Death	In Hospital MI	Recurrent Angina	CABG at Follow-up	PTCA at Follow-up	Follow-up (months)
I (n=49)	2.6+0.3 mm	70.2+6%*	88.4+4.7%**	14+4.3%	0%	0%	34%	20%	14%	18+4.1
II (n=8)	2.5+0.3 mm	87.1+3.9%*	100+0%**	100+0%	0%	71%	71%	71%	0%	19+0.7
III (n=14)	2.1+0.2 mm	63+9%*	85.+7.3%**	85+7.3%	0%	0%	33%	11%	22%	17+3.4

* p< 0.05 comparing all the groups, ** p< 0.05 comparing baseline. All the numbers are ± SD.

P1644 Stent treatment of bifurcated coronary lesions: clinical and angiographic results of a French multicenter study

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Major bifurcated lesions offer a wide variety of anatomic and angiographic features with no standardized percutaneous approach. The aim of this study was to evaluate clinical, technical and angiographic results of treatment of bifurcated coronary lesions, prospectively included in 19 centers from January to August 2001, using in all cases the same slotted tube stent (Helistent, Hexacath.). All patients (pts) had symptoms of ischemic heart disease. Bifurcated lesions were defined by a lesion located in a main vessel (MV) > 3mm including a side-branch (SB) > 2mm. Pts were pretreated with clopidogrel-aspirin. Quantitative coronary angiographic analysis (QCA) was performed off-line by an independant core-lab. Complete angiographic success was defined by a diameter stenosis < 50% in the main vessel and side branch with a normal flow.
Results: 253 pts (63 ± 11 years, 80% males) were included and 316 Helistents (250 in main artery, 66 in side-branch) were implanted in left anterior descending-diagonal (52%), circumflex-obtuse marginal (25%) and right coronary-posterior descending (23%). Six-french guiding catheter was used in 80% pts and in 67% of pts a second wire was placed in the side branch. On QCA, reference diameter of MV and SB were respectively 3.13 ± 0.36 mm and 2.37 ± 0.33 mm. Direct stenting in MV was performed in 42% of pts, kissing balloon in 41% and the T stent technique in only 25%. Despite no lesion before the procedure, the SB was compromised in 22% pts and needed subsequent PTCA. The complete angiographic success rate was 93%. Major in-hospital cardiac events occurred in 5 pts (2%; 1 death, 3 non fatal myocardial infarction, 1 rePTCA). At 6-month follow-up (93% of pts) only 1 pt died. A target lesion revascularization was performed in 26 pts (12%, including 4 bypass-grafts)
Conclusions: Despite the complexity of treatment of bifurcation lesions, this multicenter prospective study demonstrates excellent immediate clinical and angiographic results and a low incidence of target lesion revascularisation at mid term follow-up.

P1645 Coronary stenting versus stent-like balloon angioplasty: one-year clinical follow-up results

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Coronary stenting reduces the rate of angiographic restenosis and improves short-term clinical outcome. However, management of in-stent restenosis is often complex and the high cost of drug eluting stent will be an economic burden in limited ressources countries.
The aim of our study was to compare the one-year clinical outcome of patients (pts) who had a stent-like result following balloon angioplasty (PTCA) to the ones who had a coronary stenting in a non-selected population.
Methods: The results of "stent like" PTCA (post-procedural residual stenosis < 10%) in 333 pts were compared to the ones in 189 pts with stent implantation. The baseline clinical characteristics were similar between the two groups in particular with regard to diabetes(37.2% vs 38.6%, p=NS). There were more complex lesions (type B2-C) in the stent group (49% vs 25%, p<0.01).
Results: Minimal luminal diameter after the procedure was similar between the 2 groups (2.75±0.6 balloon PTCA vs 2.6±1.1mm for stent, p=NS). At a mean follow-up of 7±1 months angiographic restenosis was 35.8% after stent-like result versus 36.2% after elective stenting, p=NS.
There was no difference between the balloon PTCA and stent groups respectively with regard to the incidence of death(0.6% vs 1.5%), myocardial infarction (0.9% vs 1.5%) and target lesion revascularisation (20% vs 17%).
Conclusions: These results suggest that stent-like balloon angioplasty is a reasonable approach for the treatment of coronary lesions.

P1646 Coronary angioplasty – a real alternative to coronary artery surgery in diabetics with multi-vessel disease: a prospective registry 1998–2000

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Background Limited data from randomised controlled trials of coronary artery bypass grafting (CABG) versus coronary angioplasty (PCI) suggest better survival in the CABG arms. However, registry data from these and other studies, show that when diabetics are treated in accordance with physician preference the results are more variable.
Objective To use prospective registry data to
(a) define the clinical and angiographic characteristics of diabetics undergoing coronary revascularisation according to physician preference
(b) to report clinical outcome at hospital discharge and at one year follow-up
(c) to track any change in clinical practice pertaining to coronary intervention in diabetics over the time of the study
Methods Between January 1998 and December 2000 we prospectively identified diabetic patients with multivessel coronary artery disease undergoing cardiac catheterisation, defined as at least two vessels with narrowings of 50% or more.
Results Of 7850 coronary angiograms, 1409 (17.9%) were in diabetics of whom 739 patients had multivessel disease. CABG was performed in 230 (31.1%), PCI in 272 (36.8%) whilst 237 (32.1%) were treated medically. Angiographically, the number of diseased vessels ((mean (SD)) was significantly higher in the CABG group 2.91 (0.53) versus the PCI group 2.48 (0.53) and the medically treated group 2.73 (0.58) p<0.001. The number of vessels revascularised (mean(SD)) in the CABG group 3.15 (0.56) was greater than in the PCI group 1.36 (0.56) p<0.0001, but this difference decreased over the course of the study. Clinical differences at baseline among the groups were not marked, although there were significantly more patients managed urgently by PCI as compared with CABG. In hospital mortality was 2.2% in the PCI group and 3.5% in the CABG group. Cardiogenic shock was related to increased mortality in the PCI group, whilst significant left main stem disease (>50% stenosis) was a predictor of poor outcome in the CABG group. Rates of repeat revascularisation at one year were 23.9% in the PCI group and 2.2% in the CABG group (p<0.0001).
Over 60% of one year follow up of MACE (Major Adverse Cardiac Events) is complete and thus far one year mortality did not differ between the two groups.
Conclusion Detailed registry data can differ from that obtained from randomised trials and may give valuable insight into management decisions in high risk diabetics.

P1647 Stenting during coronary intervention improves procedural and long-term clinical outcomes in diabetics

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Diabetes is an adverse risk factor for restenosis following transcatheter intervention. Limited data is available on long-term outcomes following stenting (ST) in diabetics. We evaluated procedural and 12-month clinical outcomes following ST versus optimal PTCA in diabetics who underwent coronary intervention at our center. From 1/98 to 1/02, 1,428 diabetic patients (mean age 64 years; 45% female) presenting with acute coronary syndromes, underwent PTCA (N=911) or ST (N=517). Co-morbid factors included age >70, 32%; prior MI, 31%; prior CABG, 24%; EF <40%, 22%; multivessel disease, 18%; cardiogenic shock, 3%. ST vessels were > or =3.0 mm in diameter. Adjunctive IABP support was employed in 17.4%. Results: Procedural success (TIMI 3 flow; residual stenosis <20%) was 96% with PTCA and 99% with ST (p=0.002). CABG rate was 0.9% with PTCA and 0.2% with ST (p=0.13), with 3 (0.3%) deaths in the PTCA group (p=0.13). There was no subacute ST thrombosis in either group. At 12-month follow up, the incidence of re-PTCA (6.2% vs 4.8%; p=0.09) and CABG (4.5% vs 1.4%; p=0.88) were higher in the PTCA group but this did not reach statistical significance. Cardiac mortality was significantly lower in the ST group (1.4% vs 4.1%; p=0.04). Mean rise in LVEF was significantly higher in the ST group (4.48% vs 1.42%; p=0.04). Event-free survival was significantly higher in the ST group (93% vs 81.2%; p=0.03).
Conclusions: 1. In this large series of diabetic patients, procedural success was significantly better in coronary lesions treated with ST, compared to optimal PTCA. 2. In-hospital event rates were comparable. 3. At 1-year follow-up, absolute and event-free survival were significantly better in the ST group. 4. Long-term index lesion revascularization rates were lower with ST. 5. The ST cohort showed significant increase in LV systolic function, compared to the PTCA group. 6. In diabetics, routine stenting of coronary lesions should be considered, as acute and long-term clinical outcomes, including survival, appear to be significantly superior to optimal balloon PTCA results.

Abstract 1648 – Table

	large vessels short lesions	large vessels long lesions	small vessels short lesions	small vessels long lesions
No lesions thin:thickstrut	group I, 881 (452:429)	group II, 298 (98:200)	group III, 532 (219:313)	group IV, 151 (58:93)
Reference vessel size,mm	3.32±0.37 vs. 3.32±0.41	3.26±0.34 vs. 3.31±0.41	2.43±0.32 vs. 2.44±0.27	2.39±0.35 vs. 2.45±0.25
Lesion length,mm	8.6±3.3 vs. 8.8±3.4	20.3±5.4 vs. 21.5±5.7	8.4±3.3 vs. 8.7±3.4	19.9±5.5 vs. 21.4±5.8
Acute gain,mm	2.19±0.64 vs. 2.11±0.68	2.22±0.52 vs. 2.11±0.59	1.74±0.62 vs. 1.85±0.52	1.92±0.48 vs. 1.81±0.57
Late lumen loss,mm	0.90±0.81 vs. 1.19±0.9**	0.99±0.78 vs. 1.17±0.82	1.01±0.78 vs. 1.16±0.75*	1.18±0.72 vs. 1.16±0.85
Restenosis (>=50% DS),%	16.6 vs. 25.9 **	20.4 vs. 24.5	32.4 vs. 35.5	32.8 vs. 38.7

* p=0.02; ** p=0.001

P1648 Effect of strut thickness on angiographic restenosis rate after coronary stenting

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The study was performed to evaluate the effect of stent strut thickness on angiographic restenosis rates in different subsets of coronary vessel sizes and lesion lengths.

Methods: Coronary lesions situated in native vessels and treated with a single stent, for whom angiographic follow up was obtained, were selected for this analysis. In-stent restenotic lesions, lesions treated with radiation therapy, and chronic total occlusions were excluded. A total of 1862 lesions, from 1428 patients remained for the analysis.

Twenty-six different stent types (slotted tube and ring design) were implanted, and according to strut thickness were divided in thin-strut (strut thickness of <0.1mm) and thick-strut (strut thickness of >=0.1mm) groups.

Coronary lesions were divided into 4 groups according to various combinations of reference vessel size (Ref) and lesion length (LL): group I – Ref >=2.8mm and LL <15mm; group II - Ref >=2.8mm and LL >=15mm; group III - Ref <2.8mm and LL <15mm; and group IV - Ref < 2.8mm and LL >=15mm.

Results: There were no significant differences in baseline lesion characteristics inside groups. Procedural and follow up angiographic results for thin-strut vs. thick-strut stents are shown in table. In large vessels with focal lesions significantly higher angiographic restenosis rate was found in the thick-strut group (RR, 1.76; 95%CI, 1.26-2.44).

Conclusion: Implantation of a thin-strut stent is associated with a significant lower late lumen loss in focal lesions. In long lesions there is only a numerical difference favoring thin-strut stents. This fact could be a consequence of the smaller number of lesions or of the impact of other factors in this higher risk group.

P1649 Comparison of direct stenting with optimal balloon angioplasty: intermediate results from Polish randomized, multicenter trial

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Background: Selection of the most effective percutaneous intervention (PTCR) for patients with coronary stenoses has not been clearly defined yet. It is likely that proper PTCR guidance may improve their late results. Therefore we designed multicenter, randomized study comparing direct stenting guided with quantitative coronary angiography (QCA) or intracoronary ultrasound (ICUS) with optimal balloon angioplasty guided with ICUS or fractional flow reserve (FFR).

Methods: Till September 2001, two hundred seventy nine patients (56 F, 123M, mean age 54±9y) were enrolled into our study. They were divided into 4 groups: Gr1-direct stenting guided with QCA (80 pts), Gr2-direct stenting guided with ICUS (83 pts), Gr3- optimal balloon angioplasty guided with ICUS (96 pts) and Gr4- optimal balloon angioplasty guided with FFR (20 pts). During 6 months follow-up we recorded evidence of MACE (death, myocardial infarction, target vessel revascularisation) and in case of recurrence of angina coronary angiography was performed

Results: Procedural success was achieved in 95% of cases, however crossover to stenting was necessary in 60 (62%) patients of Gr3 and in 2 (10%) of Gr4. Periprocedural complications (abrupt vessel closure or slow flow phenomenon) occurred only in Gr3, and 11 (11,4%) patients required use of ReoPro®. QCA measurements are presented in the table below. Among studied groups, biggest balloons were used in Gr2, resulting in largest postprocedural lumen. Lowest rate of MACE and restenosis at 6 months follow up were found in Gr 2. Comparison with other groups is presented in the table.

	Gr1	Gr2	Gr3	Gr4
MLD post (mm)	3,06±0,52	3,34±0,55#	2,94±0,62	3,0±0,59
RD pre (mm)	3,19±0,54	3,21±0,64	3,28±0,62	3,16±0,69
Balloon size (mm)	3,36±0,39	3,74±0,43*	3,14±0,55	3,15±0,65
MACE (%)	11,6	6,3*	17,7	13,3
Restenosis rate (%)	25	9,1**	12	20

*p<0,001 between Gr2 and Gr1,3,4 #p<0,05 between Gr2 and Gr3,4 **p<0,05 between Gr2 and Gr1

Conclusion: Our results suggest that ICUS guided DS is coronary intervention providing the biggest postprocedural lumen gain, that is responsible for better late patients outcome.

P1650 Lesion complexity makes differences in stent performance evident: lessons from the randomized ISAR-STEREO trial

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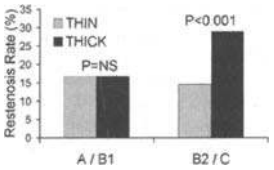
A number of stent vs. stent trials have not been able to disclose differences in stent performance at long-term follow-up. It has been hypothesized that this was caused by the inclusion of only non-complex lesions in these trials. However, the role of lesion complexity on the ability of the trial to distinguish between superior and inferior stents in terms of restenosis has not yet been investigated. The randomized ISAR-STEREO trial has shown, that reduced stent strut thickness is associated with a reduced risk for restenosis. The objective of this analysis was to investigate the role of lesion complexity to detect differences between the 2 stents tested in the ISAR-STEREO trial.

Methods: In ISAR-STEREO, 651 patients were randomized to receive either a thin-strut stent (Thin, n=326) or a thick-strut stent (Thick, n=325) with a comparable stent design. Angiographic follow-up was available in 80.6% of eligible patients (79.1 vs. 82.1% for Thin vs. Thick, p=ns). Lesion complexity was assessed using the modified ACC/AHA classification (type A to C).

Results: Non-complex (type A or B1) and complex (type B2 or C) lesions were treated in 25.3% and 74.7% of patients, respectively. The differential role of lesion complexity to detect differences in the restenosis rate between stent types is shown in the figure.



Restenosis results.

Conclusions: Significant differences in the long-term angiographic outcome were seen between thin- and thick-strut stents. These differences were only seen when complex lesions were treated. This finding may be relevant when planning new stent vs. stent trials.

P1651 Predictors of late mortality after successful coronary stent placement

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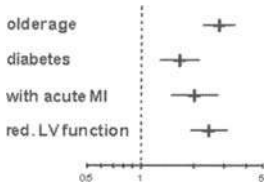
The rationale for this analysis was to identify independent clinical and angiographic risk factors for long-term mortality after successful coronary stent placement.

Methods: We evaluated all 2362 patients with successful stent placement from May 1992 throughout December 1996. A clinical follow-up at four years was obtained in >90% of patients. We analyzed 40 clinical, angiographic and procedural variables for their association with 4-year mortality, followed by a multivariate model to identify independent factors.

Results: Mortality was 1.2% after 30 days, 5.9% at 1 year, 8.0% at 2 years, 9.8% at 3 years, and 11.7% at 4 years. There were several significant differences between patients who died during follow-up compared to those alive. In particular, they were older, had more frequently diabetes mellitus, a history of CABG, a reduced LV function and multivessel disease; more frequently they were treated for acute myocardial infarction, they had higher-grade stenoses before the procedure, which were less likely located in the LAD and required more stents to achieve procedural success. In the multivariate analysis, only the variables illustrated in the graph below were identified as independent factors for 4-year mortality (illustrated by their adjusted risk ± 95% confidence interval).



Independent predictors of mortality.

Conclusions: Older age, presence of diabetes mellitus, a reduced LV function and presentation with an acute myocardial infarction are all independent risk factors for 4-year mortality. These data suggest that lesion- and procedure-related factors do not have a significant impact on long-term mortality.

P1652 Primary stenting of occluded native coronary arteries: final results of the PRISON study

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Background: Primary or elective intracoronary stent placement after successfully crossing chronic total coronary occlusions may decrease the high restenosis rate at long-term follow-up compared with conventional balloon angioplasty.

Methods: In a prospective, two-center randomized trial, standard balloon angioplasty was compared with stent implantation for the treatment of chronic total occlusions. A total of 200 patients were enrolled. Patients were followed for 12 months with angiographic follow-up at 6 months. Quantitative coronary analysis was performed by an independent core lab.

Results: Baseline patient characteristics were evenly distributed. After the procedure the mean minimal luminal diameter (MLD) in the conventional group was 2.34±0.46mm versus 2.90±0.41mm in the stented group ($p<0.001$). The 6-month angiographic follow-up showed a mean MLD of 1.57±0.74mm in the conventional group versus 1.93±0.85mm in the stented group ($p=0.009$) and a mean diameter stenosis of 44.7±25.0% versus 35.5±26.5% ($p=0.036$). Binary angiographic restenosis (>50% diameter stenosis) was seen in 33% in the conventional group versus 22% in the stented group ($p=0.137$). The reocclusion rates were 7.3% and 8.2% respectively (p=ns). At 12 month follow-up, the rate of target lesion revascularization was significantly higher in the conventional group (29% versus 13%, $p<0.0001$).

Conclusions: Primary stenting of chronic coronary occlusions is superior to balloon angioplasty alone, improving angiographic results and reducing the need for target vessel revascularization, with a trend towards lower restenosis rates. It is striking that the 6 month angiographic results of both stent implantation and balloon angioplasty are superior to the results of all previously reported trials on this issue.

P1653 Outcome after treatment of coronary in-stent restenosis: results from a meta-analysis including 3012 patients

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The aim of this study was to evaluate the clinical outcome after treatment of coronary in-stent restenosis using descriptive statistics and meta-analysis methods.

Methods: For identification of the relevant literature a MEDLINE search from 1987 to 2001 was performed with restrictions (type of study: human) using a combination of the terms "Coronary", "Stent", "Restenosis", and "Treatment". This analysis intended to include all clinical trials conducted since 1987 (a) that described a study population treated for in-stent restenosis in a randomised or non- randomised fashion; (b) that used a specified technique to treat ISR; (c) that enrolled >30 patients; (4) that included a follow-up period >3 month; (5) that provided information on the rate of major adverse cardiac events (MACE) as defined by death, myocardial infarction or target lesion (vessel) revascularisation. Based on the selected literature, a systematic review using descriptive statistics and meta-analysis methods regarding the outcome after treatment of coronary in-stent restenosis was performed. The proportion of patients experiencing a major adverse cardiac event (death, myocardial infarction, target lesion revascularisation) was defined as the main outcome measure.

Results: A total of 1304 citations were identified. Among these, 28 studies (6 different treatment modalities: ballon angioplasty, stent-in-stent, rotational atherectomy, directional coronary atherectomy, LASER angioplasty, intracoronary radiation therapy) including a total of 3012 patients met the inclusion criteria and were incorporated into this analysis. The estimated average probability of experiencing a major cardiac adverse event after treatment for in-stent restenosis with a follow-up period of 9±4 months was 30.0% (25.0%- 34.9%, 95% CI) with strong evidence for heterogeneity between study specific results ($p=0.0001$). The clinical outcome was not significantly different between treatment modalities. After adjustment for confounding factors, however, patients undergoing intracoronary radiation showed an estimated advantage of 16.9% as compared to balloon angioplasty. The postinterventional diameter stenosis was a major predictor for the long-term outcome after treatment of in-stent restenosis.

Conclusions: Treatment of in- stent restenosis is associated with an overall 30% rate of major adverse cardiac events. Currently, repeat angioplasty is recommended for focal lesions and intracoronary radiation should be considered in cases with therapy refractory forms of diffuse in-stent restenosis.

P1654 Three dimensional intravascular ultrasound imaging is superior to coronary angiography in illustrating the vessel anatomy in diabetic patients

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Background and Objective: Even though coronary angiography is the gold standard for imaging of the coronary arteries, the question remains open if coronary angiography is capable of outlining the diffusely diseased vessels in diabetic patients. We therefore aimed to compare postinterventional quantitative angiographic results with three- dimensional Intravascular Ultrasound (IVUS) imaging in diabetic patients undergoing coronary angioplasty.

Methods: Postinterventional IVUS images were obtained in 28 vessels of diabetic patients. Postinterventional minimal lumen diameter (MLD), reference diameters (RD), lengths of stenosis and percent diameter stenosis (%DS) were measured with a quantitative coronary angiography (QCA) edge-detection algorithm (ACOMPC, Siemens). Computer-assisted analysis was used to analyze the IVUS images in off-line mode (QCU-CMS, Medis). Volumetric quantification was performed by means of a semi-automated contour detection system and three-dimensional reconstruction. Volumetric measurement were performed every 0.1mm±0.05mm at the site of the lesion and at the proximal and distal reference segments. The vessel diameter and lumen diameter (VD and LD), as well as vessel area (VA) and lumen area (LA) were measured for each analyzed slice. Plaque area (PA) was calculated as VA minus LA. Volumetric plaque burden was calculated as the difference between vessel volume and lumen volume at the site of the lesion.

Results: Mean stenosis length was 13.2±4.5mm in QCA vs 17.1mm±9.0mm in IVUS ($p=0.02$). MLD was calculated as 2.56±0.54mm in QCA vs 2.4±0.5mm in IVUS (p=NS), %DS as 14.3±10.4% vs 27.23±6.5% ($p<0.001$), and VD as 3.0±0.5mm vs 4.5±0.7mm ($p<0.001$) respectively. Mean VA, LA and PA at the site of the lesion were 6.4±2.1mm^2, 16.6±3.7 mm^2 and 10.2±2.8 mm^2. Respective volumetric measurements were 275.6±129.1mm^3, 102.9±172.7mm^3, and 172.7±92.2mm^3.

Conclusion: Angiographic diagnosis of coronary arteries in diabetic patients may be distorted due to large plaque burden over longer vessel segments and resulting absence of plaque-free reference segments. This distortion is found more pronounced in QCA analysis requiring the reference diameter (i.e. for assessment of vessel diameter and %DS). In contrast, volumetric IVUS imaging is more precise in illustrating the lumen and vessel dimensions according the anatomic structures. IVUS guided coronary intervention should therefore be considered in diabetic patients for optimal evaluation of the vessel diameter.

P1655 Clinical and angiographic evaluation of small vessel stenting with "dedicated" versus conventional stents

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Background: Percutaneous coronary interventions in small vessels have less favorable outcomes in comparison with larger coronary arteries (> 3 mm), and stent implantation does not give significant benefits as shown by recent trials. In order to improve immediate and long term outcomes, new stents especially designed for small vessels, have been recently introduced in clinical practice. At present, there are not randomized trials that compare these new devices with the conventional ones.
Purpose of the study: This study randomly compares "dedicated" versus "non dedicated" stents in small vessels.
Materials and methods: At our hospital, from October 2000 to September 2001, 160 patients (pts) underwent coronary stent implantation in vessels with diameter < 2.6 mm. Patients were randomly assigned to receive either dedicated (group I) or conventional stents (group II). In group I (70 pts) the Biodivysio Small Vessel and the Multilink Pixel were used, in group II (90 pts) Multilink Tetra, Bestent 2, and Jomed stent were implanted. Acute myocardial infarction, cardiogenic shock, total chronic occlusion, and diffuse disease (lesions longer than 20 mm) have been excluded. Clinical and angiographic follow-up was planned.
Results: Clinical characteristics were similar in the two groups. Baseline reference diameter was comparable in the two groups (2.26 ± 0.3 and 2.27 ± 0.23 mm respectively). There were not diferences in minimal lumen diameter (0.64 ± 0.29 vs 0.63 ± 0.37). The acute gain resulted 1.93 ± 0.39 mm in group I and 1.89 ± 0.24 mm in group II (p 0.4). Multivessel angioplasty was performed in 25% of the cases in group I and 34% in group II (p 0.09). Procedural success was achieved in 98.7% (158/160). The incidence of MACE (death, AMI, CABG, TLR) during follow-up was 25% in group I, and 29% in group II (p 0.5). Angiographic follow-up was performed in 70% of the elegible pts. The incidence of restenosis was 26% in group I and 32% in group II (p 0.46).
Conclusions: Stents "dedicated" to small coronary arteries do not significantly improve acute and long-term outcomes, compared with conventional ones.

P1656 Stent design and stent surface material determine intimal hyperplasia. An intravascular ultrasound study on human coronary arteries

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Background: A variety of different stent designs and coatings has become available. This study sought to determine the impact of stent design and gold-coating of stents on intimal hyperplasia in human atherosclerotic coronary arteries in relationship to known procedure, lesion and patient related predictors of restenosis.
Methods: Angiographic and intravascular ultrasound (IVUS) studies were performed at 6 month follow-up on 311 native coronary lesions of 311 patients treated with 99 Multi-LinkTM stents, 74 InFlowTM steel stents, 73 InFlowTM gold-coated stents, 41 Palmaz-SchatzTM stents, 12 NirTM steel stents and 12 gold-coated Nir RoyalTM stents. Lumen and stent cross-sectional area (CSA) were measured at one mm axial increments. Mean intimal hyperplasia CSA (stent CSA - lumen CSA) and mean intimal hyperplasia thickness were calculated and averaged over the total stent length.
Results: Angiographic late loss was non-significantly different between stent types, ranging from 0.84±0.76 to 1.17±0.66 mm (p=0.131). IVUS demonstrated different levels of intimal hyperplasia for the six stents. Mean intimal hyperplasia thickness ranged from 0.20±0.13 mm for Multi-Link stents to 0.43±0.14 mm for InFlow gold-coated stents (P<0.001). Multivariate analysis confirmed non Multi-Link stent design (R^2=0.019, p=0.014), gold stent coating (R^2=0.144, p<0.001)and diabetes (R^2=0.014, p=0.041) to be the only independent predictors of IH thickness. Multivariate logistic analysis proved non Multi-Link stent design (OR=3.45, 95%CI=1.13-11.11, p<0.034) and gold coating (OR=3.78, 95%CI=1.88-7.54, p<0.001) to be the only independent predictors of intimal hyperplasia thickness greater 0.3 mm.
Conclusion: Intimal hyperplasia thickness differs significantly between different stent types. Stent design and surface material have a greater impact on the intimal hyperplasia response to stents than known procedure, lesion and patient related factors. However, the differences in intimal hyperplasia thickness between the analyzed stents are relatively small compared to the absolute lumen dimensions. Angiographic analysis fails to detect differences in late lumen loss.

P1657 Immediate and long-term outcome following the treatment of very long (>50 mm) chronic total coronary artery occlusions

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Objective: The follow-up patency rates, and the angiographic variables associated with it, after stenting of very long (>50 mm) and chronic (> 6 months) total coronary artery occlusive lesions are not well documented. Aim of the present study was to evaluate the early results and mid-term outcome following angioplasty of such lesions.
Methods: Between January 2000 and may 2001we treated 273 chronic coronary occlusions. Of these, 78 (78 patients) were in lesions [3] 50 mm long and these patients constituted the study population. Recanalizations attempts was performed iusing specific wires for total occlusions and over-the-wire ballosns in order to provide more support to guide wires and to have the opportunity to change the wire without losing the position acquired.
Results: Mean duration of occlusion was 8±2 months (range: 6 to 17 months). Procedural success was obtained in 69 (88%) patients. A total of 203 coronary stents (2.6±0.9 stent/patient) were implanted. Periprocedural MACE occurred in 7 (8.9%) patients. During a 8±2 months follow-up, 45 (58%) patients remained angina free, 3 (3.8%) had a new myocardial infarction and no death was reported. Target vessel revascularization was required in 27 (34.6%) patients. Angiographic follow-up was obtained in 61 (78%) patients. Restenosis was observed in 28 (46%) patients, of whom, 9 had reocclusion. A significant correlation was observed between the need for reintervention and lesion length (R 0.52), residual stenosis (R 0.73) and diabetes mellitus (0.68).
Conclusion: Although coronary artery stenting for very long (> 50 mm) chronically occlusive lesions is feasible, safe and is associated with a low incidence of peri-procedural adverse clinical events, these complex and expensive procedures are still associated with a high 6-month restenosis rate. Brachitherapy and drug-eluting stents might provide better long term results.

P1658 Anatomical location of lesion predicts restenosis in unprotected left main coronary artery stenting

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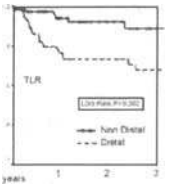
Unprotected left main (LM) coronary stenting is now an attractive alternative to coronary surgery with excellent immediate and long term outcomes in selected patients. However the impact of the anatomical location of the target lesion on clinical outcome is unknown. We set out to assess the impact of target lesion location on mortality and restenosis in unprotected LM stenting.
Methods and Results: Between Jan 1994 and Jan 2002 we performed unprotected LM stenting on 197 consecutive patients. There were 154 (78%) male patients, mean age 74±9 years, 25% diabetic, 12% renal insufficiency, mean LVEF 57±15%. The clinical indication for the procedure was: recent acute MI 14%, unstable angina 62% and stable angina 24%. The anatomical location of the target lesion in the LM was: ostial 26%, mid-shaft 19% and distal bifurcation lesions 55%. Initial procedural success was 100%. There were 16 in-hospital MACE events (7 deaths, 8 MI and 1 TLR). Follow up on 187 (98%) was completed for a mean of 23±20 months. MACE rates during follow up were as follows (33 deaths, 4 MI and 29 TLR). The freedom from TLR was: 92% and 73%, p=0.003 for non-distal and distal LM lesions respectively (Fig. 1). There was no significant difference in the incidence of diabetes between non-distal and distal groups: 33% vs 24%, p=NS. There was no difference in mortality between distal and non-distal lesions.



Kaplan-Meier freedom from TLR.

Conclusion: Unprotected LM stenting can be performed with excellent immediate and long term outcomes in ostial and mid-shaft lesions. Stenting of unprotected distal LM lesions is associated with an increased risk of restenosis and this subset of patients may benefit most from novel anti-restenosis therapies.

P1659 Effect of stent design an strut thickness on long-term outcome of coronary stent placement. Results from the ISAR-STEREO-2 trial

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Background: Stent design and strut thickness may have a significant impact on long-term outcome after coronary stent placement. The ISAR-STEREO-1 trial had compared 2 stents of very similar design but different strut thickness (ACS RX Multi-Link and Multi-Link RX Duet). A significantly lower restenosis rate was observed after placement of thinner-strut stents (ACS RX Multi-Link). Hypothesis for the multicenter ISAR-STEREO-2 trial was that the impact of strut thickness is independent of stent design.
Methods: A total of 611 patients with lesions in native coronary arteries >2.8mm in diameter were randomly assigned to either the Guidant ACS RX Multi-Link stent (strut thickness 50μm; n=309) or Cordis BX Velocity stent (strut thickness 140μm; n=302). The primary endpoint was angiographic restenosis (>50% diameter stenosis at follow-up angiography). Secondary endpoints were clinical restenosis (target vessel revascularization, TVR) and the combined rate of death and myocardial infarction at 1 year.
Results: There were no significant differences in baseline clincal and angiographic characteristics. Procedural success rates were similar (99.4% for thin-strut stents vs. 99.0% for thick-strut stents; p=0.64); yet, a difference was observed for device success rate (87.6 vs. 98.7%; p=0.09). Acute angiographic results were almost identical (final diameter stenosis, 4.3±9.7 vs. 4.2±11.6%; p=0.78). At follow-up angiography, late lumen loss was significantly lower in the thin-strut group (0.94±0.61 vs. 1.20±0.69mm; p<0.001) as well as the angiographic restenosis rate (18.9% vs. 31.6%; p=0.0002). In parallel, the TVR rate was significantly lower (12.3 vs. 21.2%; p=0.003). No difference was observed in the combined rate of death and myocardial infarction after 1 year (5.2% vs. 6.0%; p=0.67).
Conclusions: Strut thickness of coronary stents has a significant impact on long-term outcome. These data confirm that thinner strut stents are associated with lower restenosis rates, and suggest that this effect is independent of stent design.

P1660 The major profit of stent implantation is reduction of periprocedural MACE

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Reduction of restenosis rate is widely used as front argument for an increased frequency of stenting during coronary interventions. Data on this subject, however, are available only for highly selected pt. groups in randomised studies.
Between 1990 and 2001 a total of 8453 pts underwent PTCA at our institution. Out of these a total of 3050 (36%) had coronary stent implantation in the same session. During the early phase(1990-94), 289/3401 (8,5%) pts. received stents followed by coumadine/aspirin therapy. After introduction of ticlopidine as replacement for coumadine, 928/2311 (40%) of our pts received stents until 1998. From 1998 on clopidogrel was available, and 1839/2741 (67%) of our pts received stent implantation. Throughout the same time periods, the rate of periprocedural MI decreased from 2,1% to 1,6% and 0,6%, respectively(p< 0.05).Emergency CABG was necessary in 1,9% of pts during the early phase, in 1,4% in the ticlopidine era and in only 0,4% with clopidogrel (p<0,05). Restenosis rate did not change from1990 through 2001,but remained stable between 25%and 30% at angiographic follow up available for 80% of the entire cohort.
We conclude from these data, that the reduction of periprocedural MACE and not a decrease in restenosis rate is the primary advantage of stenting in larger non selected groups of pts.

P1661 Reduction of restenosis rate for direct stenting with intracoronary ultrasound guidance. Results from the prospective, randomized trial

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Background: Results of direct stenting (DS) and stenting with predilation were compared in many angiographic trials, but expected superiority of DS was not confirmed. The aim of this study was comparative analysis of early and late results of DS guided with quantitative coronary angiography (QCA) and with intracoronary ultrasound (ICUS).
Methods: Study population consists of 120 patients divided into 2 groups due to type of stent implantation guidance. There were 62 pts in DS-QCA (Gr1) group and 58 pts in DS-ICUS (Gr2) group. In Gr1 stent was sized according to QCA vessel reference diameter (RD), when in Gr2 media to media diameter measured with ICUS was used for that reason. Stent length was chosen in accordance with QCA (Gr1) and with ICUS (Gr2) measurements. Major adverse cardiac events (MACE) and target vessel revascularisation (TLR) were observed during follow-up. Coronary angiography for restenosis detection between 6-9 monts after stenting was planned.
Results: There was 100% procedural success and no early (30 days) complications in our study. There were no differences in procedural variables (max. inflation pressure & time) between two groups. Mean stent size used for DS was significantly bigger in Gr2 than in Gr1 (3,8±0,55mm vs 3,41±0,42mm, p<0,001). The need for stent redilatation was 33% in Gr1 and 39% in Gr2 (p=NS). QCA results did not differ between groups besides minimal lumen diameter obtained after procedure (2,98±0, 62 mm vs 3,35±0, 56 mm, respectively Gr1 vs Gr2, p<0,05). The evidence of MACE at 6 month follow-up was 18,4% and 10,4% for Gr 1 & Gr 2 respectively (p=NS). The control angiography revealed in-stent restenosis in 23,7% of Gr 1 and 9,3% of Gr 2 patients (p<0,05).
Conclusion: ICUS guided DS is associated with use of bigger stent size that provides better clinical outcome and lower restenosis rate.

P1662 Long coronary dissections after balloon angioplasty treated with spot stenting or entire length stenting-role of IVUS guidance

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Long coronary wall dissection after balloon angioplasty causing flow impairment is an indication for stent implantation. The aim of the study was a comparison of spot stenting vs entire length stenting with use of intracoronary ultrasound (ICUS).
Methods: Multicenter, randomized trial comparing direct stenting with optimal balloon angioplasty guided by ICUS was designed and carried out. Till December 2001 two hundred seventy four patients were enrolled into the study. Group of optimal angioplasty consisted of 96 patients. Sixty eight of them (mean age 56±10 y) after balloon dilatations presented wall dissection longer than 15 mm with flow impairment. The choice of stenting strategy was based on operator decision. Studied population was divided into two groups: Gr1 (39 pts) treated with spot stenting (SS) and Gr2 (29 pts) treated with long stenting (LS). Endpoints for the SS were MUSIC trial criteria for stented segments and at least 6,0 mm^2 for adjacent segments when for LS were at least 7,5 mm^2 along the entire length of the stent. During 6 months follow-up we recorded evidence of MACE (death, myocardial infarction, target vessel revascularisation) and in case of recurrence of angina coronary angiography was performed.
Results: Procedural success was achieved in 93% of cases. There was need for abciximab administration in 2 (5,1%) cases of Gr1 and 4 (13,7%) of Gr2. The mean length of used stents was 11,3±4,1 mm in Gr1 and 22,2±3,8 mm in Gr2 (p<0,05), but their nominal size didn't differ signifficantly between two groups (3,43±0,43 vs 3,28±0,54 mm). Angiographic and ICUS results are presented in the table 1.

	SS	LS	p
MLD post (mm)	3,45±0,65	3,54±0,72	NS
Ref.D. pre (mm)	3,01±0,43	3,11±0,53	NS
Stent area post (mm^2)	8,32±2,03	7,86±1,87	NS

During follow-up period major adverse cardiac events occurred in 4 pts (13,7%) of Gr1 and 5 pts (26,7%) of Gr2 (p=NS). Control angiography revealed a restenosis rate equal 10,3% and 21,0%, respectively; p=0,055.
Conclusions: Spot stenting of long coronary dissections with use of ICUS guidance facilitates identification of dissection entry that can be translated into clinical benefit in comparison with long stenting.

P1663 Does optimal lesion debulking need stenting?: one year follow-up results of ESPRIT

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Stenting inhibits the constrictive geometric remodeling after percutaneous coronary intervention. Cilostazol, an antiplatelet agent, is reported to control neointimal proliferation. The aim of ESPRIT (Elimination of restenosis after Stenting following Plaque Reduction with platelet Inhibitor Trial) was to evaluate the efficacy of debulking stenting followed by administration of cilostazol. Of 117 patients (pts) with a lesion successfully dilated by optimal directional coronary atherectomy (DCA) using intravascular ultrasound (IVUS), 58 pts were randomly assigned to the DCA-stent and 59 pts to the DCA alone group. Multilink stent(s) was implanted in the DCA-stent group. Medication of cilostazol (200mg/day) without aspirin was commenced after the procedure and continued until 6 month follow-up in both groups. Ticlopidine was added in the DCA-stent group for 1 month to prevent subacute thrombosis. No adverse events were observed during the hospital stay. All pts were followed up for 1 year. Eligible 6 month follow-up angiogram was obtained in 112 pts. No pts discontinued medication of cilostazol due to side effects. By 1 year, there was no death or QMI. Target lesion revascularization (TLR) was needed only in 3 pts (5.2%) of the DCA-stent and 5 pts (8.5%) of the DCA alone group. CABG was performed in 1 pt in the DCA-stent group due to refractory instent restenosis. Six month angiographic and IVUS and 1 year clinical Fu results are shown in the table. Neointimal proliferation was significantly larger in the DCA-stent group.

QCA, QCU and clinical follow-up results

	DCA-stent	DCA alone	P value
Post MLD (mm)	3.27±0.27	2.92±0.33	<0.0001
Follow-up MLD (mm)	2.53±0.59	2.41±0.69	NS
Neointima area ((mm^2)	4.2±2.4	1.5±2.8	<0.0001
TLR	5.2%	8.5%	NS

MLD = minimal lumen diameter, TLR = target lesion revascularization

Conclusion: Debulking stenting provides a larger immediate lumen, however, follow-up outcomes do not differ compared with debulking alone followed by the administration of cilostazol. These results suggest optimal lesion debulking need not always adjunctive stenting if cilostazol is administered.

P1664 Coronary artery aneurysm: incidence in 15920 patients, angiographic pattern, therapeutical options and follow-up results

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Coronary artery aneurysm (CAA) are a rare finding in patients undergoing angiography of coronary arteries (CA). The incidence varies from 0,2 to 4,9% in different sized studies. There are only case reports about therapeutical options. We report about a single center, retrospectiv analysis of 15920 patients with regard to incidence of CAA in a sequent series, to angiographic pattern, therapeutic approaches and follow up results. Between 1995 and 2000 a total of 58 (0,4%) patients with CAA could be identified. 57 (98,3%) had coronary artery disease (CAD). The CAA were predominantly (49/80,1%) found at the branches of the left coronary artery (LCA) and in the proximal third (37/63,8%) of the CA. 35 (60,3%) of all CAA were closely (< 10 mm) located to a stenosis of a CA. Of these 20 (57,1%) were located poststenotic and 10 (28,6%) in the stenotic segment. 53% of all CAA were measured between 3-5 mm in diameter. The patients showed mainly the risk factors hyperlipidemia (81%) and hypertension (61%). We could not find any relation of CAA apperance to a history of vasculitis, other aneurysmatic vascular malformations or prior therapeutic use of steroids.

The major part of all patients was treated conservativly (27/46,6%). 18 (31,6%) were sent to bypass surgery due to severe three vessel CAD. 13 (22,4%) patients were treated with percutaneus intervention (PCI) of a stenosis in the area of CAA, 4 with ballon angioplasty alone and 9 with additional Stent implantation (uncoated stents). The ballon group showed only 1 effectiv closure of a CAA, the Stent group 7 (78%) immediately and at 6 month controll. In the group of conservativly treated patients angiographic follow up in a mean intervall of 24 month documented 100% persistence of CAA without increase in size.

Summerized, CAA are a rare entity of CAD, mostly in close relation to a stenosis of a CA and often in the proximal branches of the LCA. An therapeutic strategy with PCI provides a high closure rate of CAA when Stents are used. But even in conservativ approach short time angiographic follow up showed stable CAA diameter, what may allow to monitor the natural course of the disease.

P1665 Body mass index and late outcomes after CABG and stenting for the treatment of multivessel disease: results from the ARTS trial

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Background: Obesity is associated with advanced coronary artery disease. However, the relation between body mass index (BMI) and outcome after percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) remains controversial. The purpose of the study was to assess the impact of BMI on the one-year outcomes after coronary artery revascularization in patients with multivessel disease who underwent either stent implantation or CABG.

Methods: A total of 1,203 patients with multivessel coronary artery disease, who were considered to be equally treatable with both modalities, were randomly assigned to CABG or stenting in the Arterial Revascularization Therapies Study (ARTS). The primary clinical endpoint was freedom from major adverse cardiac and cerebrovascular events (MACCE). Patients were divided into three groups according to BMI: 1) normal weight (BMI: 18.5-24.9), 2) overweight (BMI: 25-30) and obese (BMI >30).

Results: Baseline clinical characteristics were similar among the groups, except for a higher incidence of diabetes (p<0.0001) in obese patients who underwent stenting and younger age (±3 years) in obese patients who underwent surgery (p=0.009). Results are shown in the table (*p=0.04).

	Stenting			CABG		
	Normal (n=168)	Overweight (n=307)	Obese (n=124)	Normal (n=169)	Overweight (n=299)	Obese (n=136)
Death (%)	1.8	2.6	3.2	3.5	2.6	2.2
Stroke (%)	2.3	1.9	0	2.3	2.3	1.4
MI (%)	5.3	5.5	8.8	7.1	3.7	4.4
Revascularization (%)	18.4	22.4	20.9	5.3	4.3	0.7
MACCE (%)	27.8	32.4	32.9	16.5*	12.0*	7.3*

Conclusions: 1) At one-year follow-up, multivessel stenting was as safe as CABG regarding death, stroke or myocardial infarction in normal BMI, overweight and obese patients. However, the incidence of repeat revascularization was lower in CABG patients in all BMI groups. 2) Obese and overweight patients are at a lower risk of MACCE after bypass surgery compared to patients with normal BMI, but on average, they were approximately 3 years younger than their normal BMI counterparts. 3) BMI did not appear to influence the clinical outcome after coronary stenting.

PAEDIATRIC CARDIOLOGY/OTHERS

P1666 Endothelial dysfunction in patients with cyanotic congenital heart disease

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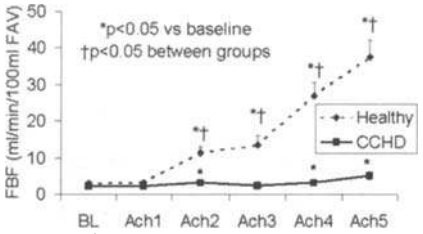
In cyanotic congenital heart disease (CCHD), secondary erythrocytosis results in increased whole blood viscosity and shear stress, causing release of nitric oxide (NO). Thus, reduced pulmonary NO production, as seen in CCHD, is not necessarily accompanied with reduced NO production in the systemic circulation. However, no data are available if vasodilation is altered in CCHD. Moreover, elevated endothelin-1 (ET-1) may contribute to increased tissue vascularity, but it is unclear if this is of importance in CCHD.

Methods: Responses to arterial endothelium-dependent (Acetylcholin [Ach]) and -independent (sodium nitroprussid [SNP]) vasodilation, NO synthase blockade (L-NMMA), ET-1 and ET-1 receptor blockade by BQ-123 of 11 CCHD patients (O2-saturation <90%, mean 79±1%, age 39±2 years) were compared with those of 10 age-matched healthy controls (HC), using forearm venous occlusion plethysmography.

Results: Resting blood flow was slightly lower in CCHD than in HC (2.2±0.4 vs 3.5±0.4ml/min/100ml forearm volume [FAV], p<0.05). While response to SNP was similar in both groups (p>.1; CCHD 2.0±0.3 to 8.3±1.0; HC 3.6±0.7 to 11.9±1.2 ml/min/100ml FAV), response to Ach was reduced (figure; p<.001). L-NMMA was less effective in CCDH (25±6% vs 40±4%, p<.05). ET-1 caused a smaller vasoconstriction in CCHD (-25±9% vs. -51±7%, p<.05), but the response to BQ-123 was similar in both groups (32±9 vs 27±9%).



Response to intra-arterial acetylcholin.

Conclusions: In CCHD, there is no vasodilation at rest, caused by reduced NO production. Although the response to SNP was not impaired, endothelial dysfunction is evident in CCHD. Due to elevated ET-1 levels, the response to exogenous ET-1 is reduced, but indicated by the similar response to BQ-123, the effects of endogenous ET-1 on arterial tone is not enhanced.

P1667 Endothelium function in normotensive patients after successful coactation repair

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Adult patients (pts) even after successful coarctation repair (SCR) suffer from relapse of hypertension and their life expectancy is shorter than normal because of premature coronary and cerebrovascular events, In previous studies we have shown that structural and functional abnormalities of the carotid arteries are present in pts after SCR. In this study we aimed at detecting the endothelium function in this category of pts as well as the inflammatory markers SVCAM-1 and SICAM-1 secreated from endothelium.

Methods: Twelve pts, 27±12 years old, 15±9 years after SCR (Group 1) and twelve matched controls selected to have the same age, sex, smoking habits, as well as lipid profile (Group 2) were enrolled in our study.

In all pts and controls were measured: SVCAM-1, SICAM-1 (ngr/ml) as well as the forearm blood flow using venous occlusion strain-gauge plethysmography. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to post reactive hyperemia blood flow. Endothelium independet flow was expressed as the % change from baseline to post sublingual nitroglycerin administration flow (NITR).

Results: FMD and SVCAM-1 were SS different in Group 1 than Group 2 (73.8±7.7 vs 117.5±15.8, p<0.05), (444.5±36.2 vs 295.6±39.1, p<0.05), respectively. SICAM-1 and NITR did not have any SS difference between Group 1 and Group 2 (258.4±15.9 vs 250.0±21.4, p=NS), (78.4±7.6 vs 88.7±11.5, p=NS), respectively.

Conclusions: From our data it is concluded that there is endothelial dysfunction in pts with SCR expressed with the investigated SS difference of the FMD in the two groups. Also the SVCAM-1 inflammatory marker is SS increased in SCR pts. These results may explain the high incidence of coronary artery disease in pts with repaired coarctation.

P1668 Prognostic value of brain natriuretic peptide in patients with complex congenital heart disease

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Background: Serum brain natriuretic peptide (BNP) has been reported to indicate ventricular dysfunction and to be an independent predictor of outcome in patients with cardiomyopathy and primary pulmonary hypertension. However, its prognostic value in patients with congenital heart disease (CHD) has not been studied, yet.

Methods: To evaluate its prognostic value, BNP was measured in 72 pts. (36 female, mean age 34 ± 12 years) with complex CHD who were followed for 17±8 months. The relation of BNP levels to NYHA functional class and ventricular function (VF) at entry as well as to the occurrence of events during follow-up in terms of death, transplantation or congestive heart failure requiring hospital admission (CHF) was analyzed.

Results: In 36 pts. with pulmonary hypertension (PHT) consisting of Eisenmenger pts. and other pts. with complex CHD and significant pulmonary vascular disease, 12 events occurred during FU (deaths 7, transplantation 2, CHF 3). BNP was significantly higher in pts. with as compared to those without events (338±254 vs 61±133 pg/ml; p<.0001). Pts. with events were on average also in a higher NYHA class (3.0±.5 vs 1.9±6; p<.0001) and presented more frequently with abnormal ventricular function (p<.005). BNP was significantly higher in pts. with abnormal as compared to those with normal VF in this group (335±270 vs 51±92 pg/ml; p<.0001). Of 12 pts. with BNP >150 pg/ml (group A; BNP 325±162 pg/ml) 10 had an event during FU (83%) whereas only 2 of 24 pts. with BNP smaller or equal to 150 (group B, BNP 31±34 pg/ml) had an event (17%). All pts. except 1 (sudden death) with events in group A developed CHF and 6 eventually died, one underwent lung transplant. Events in group B were sudden death (1) and heart lung transplantation (1). Only one pt. In group A remained stable whereas 22 of 24 pts. in group B remained stable during FU.

In 36 pts. with complex CHD but without significant PHT, no event occurred during FU. Nevertheless, 9 of them had BNP levels >150 pg/ml (325±162 pg/ml). In contrast to the pts. with PHT, in this group of pts. without PHT, BNP levels did not significantly differ between pts. with normal and those with abnormal VF (96±138 vs. 128±193; NS).

Conclusion: Serum BNP level appears to be an important predictor of outcome in pts. with complex congenital heart disease who have pulmonary hypertension. In this group, pts. with BNP > 150 pg/ml require close follow-up and intensive treatment. They may require transplantation within a short time period.

P1669 Serum soluble adhesion molecules and systemic tissue factor activation in paediatric cardiac allograft recipients

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Purpose: Chronic rejection and transplant coronary artery disease (TCAD) has a major influence on the overall mortality and morbidity in children after heart transplantation (HTx). In TCAD, there is a diffuse, concentric and sometimes rapidly progressive stenosis of the epicardial and intramyocardial coronary arteries of the graft. Interaction between the immunologically mediated alterations of the coronary artery endothelium and the activation of the intravascular coagulation system has been proposed to be an important factor.
Patients and methods: Blood samples of 52 paediatric allograft recipients (age at HTx: 7-24months, time after HTx: 6-142 months) were examined during routine follow-up at 2-4 different times. During the study period, patients did not show any signs of severe infection or acute graft rejection. The control group consisted of 65 children before elective surgery. The concentrations of soluble adhesion molecules sICAM-1 and sVCAM-1, tissue factor (TF), TF-pathway inhibitors(TF-PI) and D-dimer were determined by commercially available ELISA assays.
Results: Patients after HTx showed significant higher plasma levels of sICAM-1 and sVCAM-1 and higher D-dimer concentrations than the control group. The higher levels of TF and TF-pathway inhibitors in the HTx group did not reach statistical significance (see table).

		s-ICAM-1 (pg/ml	s-VCAM-1 (pg/ml)	TF (ng/ml)	TF-PI (ng/ml)	D-dimer (ng/ml)
Htx	mean ±SE	1045 ±35	1832 ±64	263 ±43	65.2 ± 5.2	760 ± 74
	range	111-3534	492-4540	20-5480	8-470	139-5260
controls	mean ± SE	797 +/ 34	1191 ± 49	208 ±21	57.4 ± 4.8	356 ± 90
	range	62-1200	561-2643	80-425	18-123	124-2620
p-value		<0.000	<0.0001	n.s.	n.s.	<0.01

60% of the patients with hypertrophy of the left ventricular posterior wall or of the septum also showed increased sVCAM-1 levels. Furthermore patients with more than 2 acute rejections demonstrated significantly higher levels of sVCAM-1. Multiple regression analysis revealed a significant correlation between TCAD and maximum sICAM-1 and D-dimer levels (r=0,4, p<0,05).
Conclusion: These findings suggest an increased interaction between the activated endothelium and the intravasal coagulation system as a relevant process in paediatric HTx and TCAD development.

P1670 Normal left ventricular anatomy and its variants as classified by second harmonic echocardiography

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Two-dimensional transthoracic echocardiography (2DTT) is the standard and routine technique for anatomic and functional evaluation of the left ventricle (LV). Over the last 5 years advancements in transducers, and introduction of high resolution and second harmonic technology improved the evaluation of LV anatomy and in particular endocardial surface at the mid and apical levels. The "old" echocardiographic description of the LV cavity might be re-written on the basis of this new technology trying to better define the normal anatomy of the LV endocardial surface and to describe anatomical variants such as apical false tendons and apical trabeculations. We included in this study 1252 adult consecutive patients undergoing 2DTT (second harmonic and high-resolution technology) for various pathologies. Images were stored in magneto-optical disks and reviewed by two independent experts; "anomalous apical images" (AAI) were classified as: false tendons (FT: number, site and diastolic length), abnormal trabeculations (TR: site and systolic TR/left ventricular wall thickness ratio, TR/LVWT), apical thrombi (TH: site and area). AAI were observed in 555 out of 1252 cases (44,3%); the majority of AAI were FT (81,1%), while TR were found in 16%, TH in 2,4%, FT+TR in 16% and FT+TH in 0,5% of cases. To better define the incidence of these AAI in the study population, cases were divided into two groups: normal LV (normal size, dimension and systolic function) and pathological LV (5 categories: dilated LV, hypertrophied LV, inferior/lateral akinesis, anterior/septal akinesis, valve disease). Incidence of AAI was significantly greater in pathological LV (466/863, 53,9%, with higher prevalence in dilated hearts and apical infarctions) than in normal LV (158/389, 40,6%). No differences in age, LV end-diastolic volume or ejection fraction were found in patients with and without AAI; AAI were more frequently in male (344/706, 48%) than in female (201/529, 37,9%,) FT were isolated in 73%, while two (24%), three or more FT were less common. Their lenght was 3 ± 1 cm and these structures transverse the LV cavity (septum to lateral wall) in the majority of cases. TR were more frequently found at the apical-septal or apical-lateral site; TR/LVWT was 1,4:1. These preliminary data confirm a high prevalence of AAI in patients with and without pathological hearts suggesting the need of updating LV anatomy in the light of these new echocardiographic findings.

P1671 Discrete subvalvular aortic stenosis (DSAS) – Pitfall in the diagnosis of patients with hypertrophic obstructive cardiomyopathy (HOCM)

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Introduction: Generally, diagnosis of typical HOCM with subaortic obstruction and dynamic pressure gradient accross the left ventricular outflow tract is made by non invasive diagnostic procedures with great certainty by employing transthoracic and/or transoesophageal echocardiography. However, in pts. with asymmetric septal hypertrophy additional discrete subvalvular membrane may be a potential pitfall in the diagnosis of HOCM as it is described in several casuistic reports in the literature. The exclusion of DSAS is of special importance in pts. referred for catheter interventional therapy. To date systematic investigations concerning the frequency of DSAS in symptomatic pts. referred for catheter interventional therapy of HOCM are lacking.
Methods: Therefore, we investigated for the first time in a systematic study 180 consecutive symptomatic (functional class III-IV according to NYHA) pts. with HOCM who were referred for this new catheter interventional therapy. In all pts. transthoracic echocardiography (TTE), bicycle exercise Doppler echocardiography and multiplane transoesophageal echocardiography (TEE) were performed.
Results: In 4 of 180 pts. (2,2%) the diagnosis of DSAS (4 pts.; 3 female pts. and 1 male pt.; age 41 years, range 20 to 58 years; functional class III according to NYHA; mean septal diameter 19 mm) was made. 3 of these pts. belonged to the membranous type of DSAS; in one pt. a tunnel-like form of DSAS was present. In all cases the diagnosis could be confirmed by surgical treatment. TEE evaluation was of crucial importance with demonstration of a typical subvalvular membrane (in 3 pts.) which was situated a few millimeters below the aortic valve. In all cases a typical asymmetric septal hypertrophy mimicking HOCM was seen. A Sam-like motion was demonstrated in all 4 cases. However, only in one pt. a Sam-septal contact was present. In one of these 4 pts. DSAS could be identified definitely only after shrinkage of the intraventricular septum due to catheter interventional therapy with persisting gradient.
Conclusion: The frequency of DSAS in symptomatic pts. referred for HOCM is unexpectedly high (approximately 2,5%). Especially in pts. in whom TTE evaluation is of insufficient quality, investigation employing multiplane TEE with careful evaluation of the small poststenotic subvalvular area in HOCM is of crucial importance in diagnosing and classifying DSAS (membranous type, fibromuscular ring, tunnel type). This is of special importance because DSAS can only be treated by surgery.

P1672 Persistence of left ventricular hypertrophy in normotensive adult survivors of coarctation repair in childhood

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Objectives: To investigate the prevalence of left ventricular hypertrophy (LVH) in normotensive adult survivors of aortic coarctation corrected in childhood as assessed by transthoracic echocardiography (TTE) and 24 hour ambulatory blood pressure monitoring (ABPM).
Methods: Concurrent TTE and ABPM were undertaken in 19 patients with corrected coarctation and a clinic systolic blood pressure (SBP) <140mmHg, recruited consecutively from the Adult Congenital Heart Disease Clinic. All patients had undergone their first intervention more than 10 years previously. Population normative data, corrected for body surface area, were used for comparative purposes for TTE data, and age- and sex-matched normotensive controls for the ABPM parameters.
Results: There were no significant differences in any standard ABPM parameter among the 19 patients and 19 controls (average daytime SBP<135mmHg) although a non-significant trend toward a reduction in day-night systolic variation was noted. Adequate TTE images were obtained in 16 patients; 5 males, median age 32.5 years (range 28-48). Left ventricular (LV) posterior wall diameter (diastole) was greater than 11 mm in 4 (25%) patients, all of whom had concentric LVH. Septal dimensions were increased in a further 5 patients (56% in total). LV mass index was increased in 4/5 males and 8/11 women. LV ejection fraction (Simpson) and fractional shortening were normal in all but one patient. Diastolic function as assessed by mitral inflow Doppler studies was normal in all patients (E:A ratio 1.3-2.5). Isovolumetric relaxation time was prolonged in only 2 patients, both of whom had concentric LVH and increased LV mass.
Conclusion: Left ventricular hypertrophy and increased left ventricular mass, assessed echocardiographically, are very common in adults after successful coarctation repair in childhood. This does not seem to be as a result of persistent systolic hypertension and deserves further investigation. The presence of LVH implies a poorer prognosis in other fields of cardiology - implications for this large patient group are, of course,unknown. Further studies, both in terms of mechanism and outcome, are indicated.

P1673 Global autonomic nervous system impairment late after the Fontan operation

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Background: Arrhythmias is the most common complication late after the Fontan (F) operation. Although heart rate variability (HRV) and baroreflex sensitivity (BRS) are independent markers of autonomic nervous system (ANS) activity and strong predictors of sudden cardiac death in other cardiovascular disease, little is known about their role in adult patients with F operations.
Methods: We measured HRV and BRS in 23 patients late after F repair (9 male, age 27±9y, 14±7y after repair) and in 23 age- and sex-matched normal controls (30±8y, p=0.2 vs F). All subjects underwent 20min of resting measurements of heart rate (ECG) and non-invasive beat-to-beat systolic blood pressure (SBP). A 5min period of 0.1Hz controlled breathing was also recorded. BRS was computed by: a) the a-index (square root of the ratio between RR interval and SBP spectral powers in the low (0.04-0.15Hz, a-LF) and high frequency (0.15-0.4Hz, a-HF) bands, b) the ratio of the average amplitude of oscillations in RR interval and in SBP during controlled breathing (BRSCbr) and c) the sequence method (linear regression slope of RR interval vs SBP, BRSseq). Time domain (SDNN, RMSSD, triangular index) and frequency domain (LF, HF) HRV variables were also measured. Age at F, years from F, and antiarrhythmic therapy (AT) were taken into account.
Results: All HRV and BRS indices were markedly impaired compared to controls (table). Within the F group, BRS and HRV measures did not relate to age at F, years from F and AT.

mean value (SD)	Fontan (n=23)	Control (n=23)
log SDNN	1.5 (0.3)	1.9 (0.2)**
log RMSSD	1.4 (0.4)	1.8 (0.2)*
Triangular index	121 (74)	297 (91)**
log LF	1.9 (0.8)	2.8 (0.4)**
log HF	1.9 (0.8)	2.8 (0.4)**
log a-LF	0.7 (0.4)	1.1 (0.2)**
log a-HF	0.9 (0.4)	1.4 (0.2)**
log BRSSeq	0.9 (0.3)	1.3 (0.2)**
log BRSCbr	0.8 (0.3)	1.3 (0.2)**

Unpaired t-test: *p<0.01, **p<0.0001

Conclusions: There is a global impairment of ANS regulation late after the F operation that may have prognostic implications in these patients.

P1674 Reduced cardiopulmonary exercise performance after tetralogy of Fallot repair is not related to resting central haemodynamics assessed with MRI

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Introduction: Adults with repaired tetralogy of Fallot (rToF) have reduced exercise capacity. This has been mainly attributed to pulmonary regurgitation (PR). We aimed to investigate any relationship between cardiopulmonary exercise performance indices and resting haemodynamics assessed noninvasively with MRI.
Methods: Cardiopulmonary exercise test was performed in 94 consecutive patients with rToF aged 32±11years (range16-57). Ninety patients underwent MRI on the same day for determination of biventricular volumes, mass, EF and pulmonary regurgitant fraction (PRF). Patients with a respiratory quotient <1 at peak exercise (*n*=18) were excluded. Values obtained for oxygen consumption at peak exercise (peakVO2), anaerobic threshold (AT) and VE/VCO2 slope, were also expressed as percentage of age and sex-matched predicted values.
Results: (table) PeakVO2 in patients was 81±20% of predicted. Percent predicted peakVO2 (%peakVO2) was inversely correlated with PRF (r=-0.4, p<0.01) and the number of reoperations on the right ventricular outflow tract (RVOT) (r=-0.4, p=0.05). PRF was the only independent predictor of %peakVO2 (multiple regression: b=-0.004, p=0.003). There was no correlation of peakVO2 or %peakVO2 with biventricular volumes, EF, or mass.

	Min	Max	Mean	SD
Years after repair	7	39	24	8
peakVO2	13.1	74	30.4	9.3
%peakVO2	40	168	81	20
VE/VCO2slope	13.8	42.3	27.7	6.7
%VE/VCO2slope	48	180	100	24
AT	9	30	18.6	5.1
%AT	17	152	84	24
%Heart rate	65	111	90	11

Conclusions: Cardiopulmonary performance in adults with rToF is reduced. PR and RVOT reoperations have a negative-albeit weak- association with exercise capacity. However biventricular volumes, EF and mass as assessed by MRI do not relate directly with exercise aerobic capacity. Assessment of central haemodynamics during exercise may offer better insight into the mechanisms of reduced exercise capacity in this population.

P1675 Restrictive right ventricular physiology predicts superior exercise hamodynamics in surgically corrected tetralogy of Fallot patients

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Conflicting reports on the effect of restrictive right ventricular (RV) physiology affecting exercise capacity in surgically repaired tetralogy of Fallot (rTOF) patients have been reported. Restrictive RV is defined as positive flow seen in the base of the pulmonary artery during late diastole coincident with atrial contraction due to the right ventricle being restrictive the, impulse of atrial contractions continued into the pulmonary artery as a result of forward displacement of the pulmonary valve. This is therefore reflected as a positive wave during late diastole. We sought to see the relation between exercise haemodynamics and restrictive Vs non-restrictive RV Vs normal controls. The patients underwent formal cardiopulmonary exercise testing with assessment of exercise haemodynamic parameters
Results are expressed as mean ±SEM. 23 rTOF patients, of which 13 had restrictive RV physiology, were compared 11 against aged matched controls. Both the restrictive and non-restrictive rTOF groups had reduced exercise duration (8.70±2.86mins Vs 13.51±2.67mins, p<0.001). The non-restrictive group had significantly prolonged QRS complex (140±32.66ms Vs 84.55±12.14ms, p<0.001), higher Ability Index (1.7±0.82 Vs 1±0.00, p<0.05) and reduced peak oxygen consumption (26.90±7.35ml/min/kg Vs 36.21ml/min/kg, p<0.03), peak exercise cardiac output (11.63±3.53l/min Vs 16.58±3.91l/min, p<0.01), cardiac reserve (6.44±2.18l/min Vs 10.05±3.40l/min, p<0.01), peak exercise cardiac power output (2.84±0.98W Vs 4.05±0.89W, p<0.02) and cardiac power reserve (1.83±0.79W Vs 2.65±0.71W, p<0.03). There was no significant difference between the control group and the restrictive group in any of the above parameters of exercise haemodynamics.
Conclusion There was no difference in exercise haemodynamics between the two-rTOF groups however non-restrictive RV physiology was associated with reduced exercise duration and haemodynamics along with a prolonged QRS complex compared to the normal population. This suggests these patients have impaired cardiac function and therefore a reduced prognosis.

P1676 Progressive aortic root dilatation in adults late after repair of tetralogy of Fallot

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Background: Aortic root dilatation has been previously reported in patients with repaired tetralogy of Fallot.
Methods: We studied 56 consecutive adults with repaired tetralogy of Fallot aged 36±10 years (range 18-62 years, 21 females and 35 males) with cross sectional echocardiography. Median age at repair was 8 years (range 1.5-51 years). Measured indices were compared with those derived from echocardiograms performed at least 30 months previously (50±13 months, range 30-77 months) at our institution. All patients were over 15 years old at first study. A single blinded investigator performed all measurements. Aortic root diameter was measured on standard long axis parasternal 2-D images. Left ventricular dimensions and function were assessed on long axis parasternal M-mode views.
Results: 2-D aortic root diameter increased significantly over time at the level of the sinuses of Valsava (Ao2) (3.61±0.71cm vs 3.85±0.76cm, p=0.0002) and at the sinotubular junction (Ao3) (3.44±0.75cm vs 3.76±0.78cm, p=0.0002), but not at the level of the aortic valve (Ao1) (2.75±0.66cm vs 2.92±0.63cm, p=0.09). There was no increase in aortic regurgitation or any change in left ventricular dimensions and function with time. There was a weak but significant positive correlation between age at repair and aortic root size at the first (Ao1: r=0.616, p<0.0001; Ao2: r=0.492, p=0.0002 and Ao3: r=0.382, p=0.02, respectively) and current echocardiogram (Ao1: r=0.458, p=0.0006;Ao2: r=0.382, p=0.005 and Ao3: r=0.371, p=0.009, respectively).
Conclusions: Aortic root size relates to age at repair suggesting that increased aortic flow prior to repair might be responsible for aortic root dilatation. Furthermore, there is ongoing aortic root dilaation late after repair of tetralogy of Fallot. Prospective follow-up is needed for determination of the significance of our findings.

P1677 Right ventricular function in patients with transposition of the great arteries and atrial switch operation: tissue Doppler evaluation

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Background: The major clinical problem associated with the atrial correction for complete transposition of the great arteries (=TGA) is the development of right ventricular (=RV) failure. The evaluation of the RV by echocardiography (=Echo) is limited by the complex shape of the RV. The estimated ejection fraction (=EF) by Echo often does not correlate with the patients symptoms. Tissue Doppler (=TD) has the potential to estimate systolic function, irrespective of visualisation of the whole ventricle.
Methods: In 40 patients with TGA (mean age 21.6 ± 2.8 years) echo was performed to evaluate regional myocardial function by TD and global ejection fraction of the RV. All patients received a cardiopulmonary exercise test the same day to determine peak oxygene uptake (=peak VO2).
Results: Mean peak VO2 was 28.2 ± 6.7 ml/kg/min; mean EF was 43 ± 9.6%; mean systolic velocity of the basal lateral RV- segments was 7.5 ± 2.5 cm/s. There was no significant correlation of EF and peak VO2. The maximum systolic myocardial velocities correlated positively with the peak VO2 ($p<0.05$; $r=0.66$).
Conclusion: TD of the RV correlates with cardiopulmonary exercise capacities in patients with TGA. TD was a more accurate method in the evaluation than ejection fraction.

P1678 Pulse pressure as a risk factor of the injury of the systemic right ventricle after atrial repair of transposition of the great arteries

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Background: There is a discussion on how patients with complete transposition of great arteries (TGA) with systemically functioning right ventricle after atrial switch should be treated, and whether and when prevention of right ventricular dysfunction is warranted. Hence we analyzed the association between pulse pressure (PP) and blood pressure (BP) at rest and exercise during treadmill exercise test and function of the systemic ventricle.
Methods and Results: The studied population consisted of unselected patients with simple TGA 11.5±2.7 years after atrial switch procedure. All patients had BP values (systolic 109.1±11.7 mm Hg and diastolic 72.3±9.7 mm Hg)well within the thresholds for normal systemic circulation. Patients were divided into subgroups according to the severity of systemic ventricular dysfunction (EF <=0.40 vs >0.40), the occurrence of perfusion abnormalities in radionuclide study (absent or mild vs moderate-to-severe) and the degree of systemic venous valve regurgitation (absent-to-mild vs moderate-to-severe). Mean EF in the first pass angiography was 0.36±0.07, ranging from 0.20 to 0.53, moderate-to-severe perfusion abnormalities were detected in 21 patients (35.1%, moderate to severe systemic venous valve regurgitation in 12 (20%). When BP values together with clinical variables were entered into a multivariate backward logistic regression model with EF as a dependent value, PP at rest, as well as systemic venous valve regurgitation remained in the equation with the Chi square of 19.414 at p level of 0.0001; with systemic venous valve regurgitation as a dependent value, age and diastolic BP at exercise remained in the equation with a Chi square of 25.175 at p level of <0.0001; with perfusion abnormalities as a dependent value, body surface area and systolic BP at rest remained in the equation with a Chi square of 9.668 at p level of <0.008.
Conclusions: In "normotensive" TGA patients with systemically functioning morphologic right ventricle after atrial switch procedure there was a significant correlation between BP and PP values both at rest and exercise and systolic dysfunction, perfusion abnormalities and severity of systemic atrio-ventricular valve regurgitation. This further supports the point that unloading therapy, even within the normal range of BP values, might be warranted.

P1679 The degree of tricuspid insufficiency is a useful indicator of perfusion and function of the systemic ventricle in complete transposition

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Background: One of the late problems associated with the atrial correction for complete transposition (TGA) is right ventricular (RV) failure. The purpose of our study was to assess whether echocardiographically evaluated tricuspid regurgitation (TR) is a useful indicator of the functional status of the systemic RV in TGA.
Methods: 60 patients (14.9±14.5 years old) with simple TGA, 11.5±12.7 years after Mustard or Senning operation were included in the study. Echocardiographic examination and myocardial perfusion imaging at rest and exercise were performed on the two successive days of the study. RV ejection fraction (RVEF) was calculated from background-corrected end-diastolic and end-systolic counts of the first-pass angiogram. TR was classified as mild or moderate-to-severe using a standard semiquantitative Doppler method.
Results: 48 (80%) patients had mild and 12 (20%) moderate-to-severe TR. TR correlated significantly with RVEF (-0.30; $P<=0.03$), QRS width (0.45; $P<=0.001$), cardiothoracic ratio (0.39; $P<=0.02$), body surface area (0.27; $P<=0.04$) and age at surgery (0.44; $P<=0.001$). Patients with moderate-to-severe TR had lower RVEF (0.30 vs 0.36; $P<=0.01$) and tended to have more frequently significant perfusion abnormalities at exercise (28% vs 8%; $P=0.056$), compared to patients with mild TR.
Conclusion: TR was a simple indicator of the functional status of the systemic ventricle in TGA. Significant TR was associated with the depressed systolic RV function and increasing perfusion abnormalities in patients after atrial switch procedure for TGA.

P1680 Ventilatory response and pulmonary gas exchange at rest and during exercise in patients after the Fontan operation

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Background: Although abnormal pulmonary circulation, lung function and respiratory response during exercise are well known characteristics in Fontan patients, the relationships between these impaired functions have not been well established.
Methods and Results: Pulmonary function and cardiopulmonary exercise tests were performed in 95 Fontan patients (mean age = 13.6 years, atriopulmonary connection in 29, total cavopulmonary connection in 66) and 44 controls. Vital capacity (VC) and diffusion capacity were significantly lower in Fontan patients than in controls. VC was associated with the number of surgical procedures and decreased significantly during follow-up, being significantly related to the higher frequency and smaller tidal volume (respiratory pattern) during exercise, while did not relate to the dead space ventilation (VD/VT), ventilatory equivalent for CO_2 production (ventilatory efficiency) or peak oxygen uptake. Rest and exercise minute ventilation was accelerated and the VD/VT was higher during exercise in Fontan patients. Lower arterial saturation was related with accelerated ventilation, resulting lower resting $PaCO_2$ and resting arterial gas tensions and alveolar ventilation to CO_2 production ratio, not the types of repair or VC, determined PaO_2 and $PaCO_2$ dynamics during exercise. Fontan patients with left ventricular type had higher diffusion capacity, superior ventrilatory efficiency and peak oxygen uptake compared with those without.
Conclusions: After the Fontan operation, progressive restrictive ventilatory impairment determines the exercise respiratory pattern. Resting slight but significant hypoxia and high VD/VT during exercise have a great impact on accelerated ventilation. However, the ventricular morphology rather than the lung volume or respiratoty pattern have a greater impact on not only their exercise capacity but exercise ventilatory efficiency.

P1681 Cardiomyopathy in Alstrom syndrome

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Purpose: Alstrom Syndrome (AS) is a rare recessive genetic disorder located on chromosome 2p13. Cardiomyopathy in childhood has been described in AS, but the frequency and natural history are unknown.
The cardinal features of AS include infantile nystagmus and photophobia, with early visual loss (retinal pigmentary degeneration), sensori-neural deafness, childhood truncal obesity and insulin resistant diabetes mellitus. Intelligence is usually normal. Additional metabolic problems may occur. Late diagnosis is common since several cardinal features only become apparent with time.
Methods: In this study we identified patients with AS through referrals to a specialist genetic centre, by contact with the website for Alstrom Syndrome and through the Society for Alstrom Syndrome Families. Patients were included if the standard diagnostic criteria were confirmed by review of the patient and/or their medical records, (supplemented by data from a structured medico-social questionnaire completed by 65 patients and families).
Results: We identified 122 patients with AS, ranging in age from 14 days to 48 years, with an equal sex ratio. Over half the patients had experienced childhood cardiomyopathy [74/122 (60%)].Typically, acute heart failure developed in infancy, between the age of 2 weeks and 10 months (median onset 2 months). Although 12/54 died (22%), all but 3 of the survivors made an apparently full recovery. However, on long-term follow-up, 9 (21%) have subsequently developed dilated cardiomyopathy (age at relapse 5 - 36 years, median 16). There were 20 AS patients in whom heart failure was not apparent until after infancy (onset age 2.5 - 36 years, median 11 years). This group appear to have a more typical progressive dilated cardiomyopathy with a higher mortality rate (10/20, 50%).
The remaining AS patients are so far free from cardiac disease at follow-up, age 7 months to 48 years.
Overall, 33/122 (27%) of the patient group have died, 23 from cardiac disease, 6 from non-cardiac disease and 4 infants from unknown cause.
Conclusions: 1. Childhood cardiomyopathy affects over 50% AS patients and is the main cause of premature death.
2. AS patients need lifelong cardiac evaluation with a high index of suspicion for cardiac involvement.
3. Greater awareness of the association between infantile cardiomyopathy and the distinctive eye signs will enable earlier diagnosis of AS.

P1682 Early surgical treatment of infective endocarditis in congenital heart diseases. Outcome and prognosis

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The aim of this retrospective study was to determine the prognostic significance of early surgical treatment for infective endocarditis (IE) in patients with congenital heart diseases (CHD).
From 1966 to 2000, 167 IE occurred in 153 pts, aged 3.6days to 78.5years(y) (median 10y); 125 were <18y of age and 42 were adults. Underlying CHDs were: ventricular septal defect isolated (15%: repaired 24%, unoperated 76%) or not (8%: repaired 60%), complex cardiopathy cyanotic (18%: palliated 77%) or acyanotic (7%: palliated 33%, non-operated 41%), Tetralogy of Fallot (8%: repaired 50%, palliated 36%), aortic (9% including bicuspidia 2.4% and prothesis 4%) or mitral (7% including MVP 2.4%, non-operated 100%) valvulopathies, and ductus arteriosus (2 non-operated), atrial septal defect + mitral anomaly (3= 2 repaired, 1 non-operated), pulmonary stenosis(1 non-operated). Route was unknown (31%), dental (25%), post cardiac surgery (19%), cutaneous (9%), ENT (6%) or other. Blood cultures were negative in 14%; streptococcus and staphylococcus were the commonest agents. Clinical cardiac complications occurred in 26%, embolias in 31%. Vegetations were the most frequent echographic lesion (42%). Early surgery (< 3d month after diagnosis) occurred in 31% of the cases and was indicated for haemodynamic instability, uncontrolled sepsis or multiple embolias. Risk factors for early surgical treatment were: underlying CHD (mitral and/or aortic valvulopathy, p=0.0008), clinical cardiac failure (p<0.0001), embolias (p= 0.0014), extracardiac complications due to embolia (p= 0.0026), site of IE (mitral and/or aortic, p<0.0001), echographic lesions (vegetations, p<0.0001). Age, period, time to diagnosis, bacterial agent were not significant factors. Early surgical treatment included mitral and/or aortic prosthesis (50%), mitral repair (8%), valvular homografts (8%), Ross operation (8%), interventricular patch (11%), ductus ligation (2%) and miscellaneous. Thirty-four patients died (21%), 1 day to 19.5y after diagnosis (median 6mths), from post-IE (48.5%), cardiac non-IE (39%) or unknown (12%) causes. Survival was 93%, 89%, 87%, 76% and 56%, at 1mth, 6mths, 1y, 10y and 25y. Early surgical treatment did not influence mortality nor survival.
Our results show that left heart cardiopathies and locations, clinical complications and echographic vegetations lead more often to early surgery without increase in mortality.

P1683 Comparative rate of haemodynamic progression of discrete subaortic and right mid-ventricular obstructions in adults. Management implications

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Background: Discrete subaortic stenosis (DSS) and right mid-ventricular obstruction (RMVO) represent unique cardiac lesions, as they do occur very infrequently in neonatal period and might progress in severity during lifetime. The purpose of this study was to compare the rate of progression of these two entities during adulthood in an attempt to make clear the indications for surgical management.
Methods and Results: The clinical and echocardiographic findings in 93 adults with DSS (mean age 36 ± 19 years) and 25 adults with RMVO (mean age 26 ± 6 years) who survived into adulthood without previous intervention have been retrospectively analyzed and compared. The relationship between peak pressure gradient (PPG) and age was analyzed. Mean change in PPG with time was determined in those patients with two or more available Doppler echocardiographic examination performed with at least a two-year interval. A significant correlation between PPG and age was found in DSS (r=0.61, p<0.001) and RMVO (r=0.63, p=0.001) but the slope of regression was steeper in RMVO (y=3.4x, 95% confidence interval [CI] 1.5 to 5.3) than in DSS (y= 1.3x, 95% CI 0.94 to 1.65). Peak pressure gradient increased from 39.2±28 mm Hg to 46.8 ± 34 mm Hg (p=0.01) during a mean follow-up of 4.8±1.8 years in 25 patients with DSS and from 31 ± 26 mm Hg to 67 ± 35 mm Hg (p<0.001) during a mean follow-up of 6.17 ± 2.7 years in 13 patients with RMVO. The slope of the change in PPG was also steeper in RMVO (6.1 ± 3.0 mm Hg per year) than in DSS (2.25 ± 4.7 mm Hg per year).
Conclusions: Both DSS and RMVO show a progressive nature along the adult life, but the rate of progression is slow in DSS and accelerated in RMVO. These data suggest a more conservative surgical approach in DSS than in RMVO.

DIABETES AND CARDIOVASCULAR DISEASE

P1684 Diabetes leads to less contractile reserve after myocardial infarction

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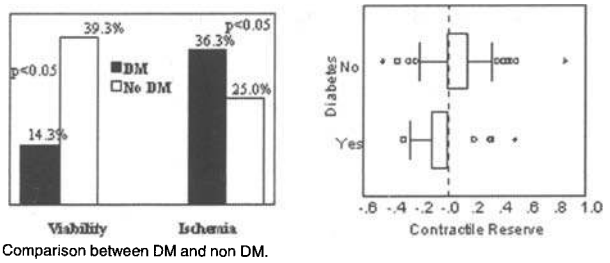
Although several reasons for the worse prognosis of acute myocardial infarction (AMI) in diabetic (DM) patients have been recognized, left ventricular ejection fraction seems not to be lower in DM. The aim of this study was to evaluate whether, although having a similar left ventricular ejection fraction at rest, DM patients with AMI have a reduced left ventricular contractile reserve in comparison with non-DM.
Patients and methods: 108 patients were included in the study after having suffered an AMI. Low-dose dobutamine echocardiography was performed, beginning at 5 ìg/kg/min and increasing the infusion rate every 3 min up to 20-40 ìg/kg/min. Contractile reserve was considered to be present when systolic function improved at least in one degree during dobutamine infusion in hypoquinetic or aquinetic segments. Patients with (28, 25.9%) versus without (80, 74.1%) DM were compared.
Results: Mean age was 66±10 yr, and 91 (84.3%) were male. Out of the 108 patients, 28 (25.9%) were DM and 80 (74.1%) non DM. Baseline left ventricular wall motion index was not different between DM and non DM (1.67±0.44 vs. 1.60±0.39, p = NS). In 33 of the 108 patients (30.6%) contractile reserve (myocardial viability) was present, and 31 (28.7%) showed ischemia during dobutamine echocardiography. Importantly, the presence of myocardial viability was significantly less frequent in DM than in non DM (14.3% vs. 36.3%, p = 0.033) (see figure).



Comparison between DM and non DM.

Conclusion: Although having a similar left ventricular systolic function at rest, the presence of contractile reserve after AMI is less frequent in DM patients in comparison with non DM. This could contribute to the poorer prognosis of DM when suffering an AMI in comparison with non DM.

P1685 Presentation of fluid retention in diabetic patients with chronic heart failure using thiazolidinediones

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Background: Insulin resistance and poor glycemic control adversely affect prognosis of chronic heart failure. Thiazolidinediones (TZDs) appear to have a remarkably potent and beneficial effect on endothelial function in addition to improving insulin sensitivity. However, TZDs are contraindicated in patients with heart failure due to their propensity for fluid retention, although the characteristics of patients with heart failure and fluid retention remain poorly understood.
Methods: We identified patients with chronic stable heart failure (NYHA I-III, EF ≤45%) and diabetes mellitus who are referred to the Cleveland Clinic for heart failure management, in which TZDs (troglitazone, pioglitazone or rosiglitazone) have been previously initiated. Retrospective chart review is performed to evaluate for baseline ejection fraction and glycemic control prior to TZD initiation, as well as changes in weight and clinical course at the end of 6 months following TZD therapy. Fluid retention is defined as involuntary weight gain (>10 pounds over 6 months) with clinical evidence of fluid overload. Univariate analyses using t- and chi-square tests comparing demographic and echocardiographic variables between the upper tertile(GAINERS) and lower tertile(NON-GAINERS)of weight changes are performed to identify clinical predictors for fluid retention following treatment with TZDs.
Results: Of the 111 consecutive patients (mean age 55 ±9 years, 68% male, mean LVEF 28.9 ±7%) identified, the mean change in weight over 6 months of TZD therapy is 5.9 ±8 pounds. GAINERS (mean weight gain 14.1 pounds) are significantly differed from NON GAINERS (mean weight gain 0.6 pounds) in larger body mass index, more females and less treated with insulin. Weight gain is independent of the baseline severity of heart failure (either by ejection fraction or by NYHA class). Overall, 17.1% patients present with refractory fluid retention (>10 pounds despite intensified diuretic therapy) mimicking decompensated heart failure within 6 months following TZD initiation. Only 2 patients have clinical evidence of pulmonary edema and none have significant hepatotoxicity. Following TZD discontinuation, all have resolution of their fluid retention.
Conclusion: Presentation of fluid retention following treatment with TZDs in diabetic patients with systolic dysfunction may mimic heart failure decompensation. This manifestation is reversible following TZD withdrawal. However, no direct association can be made between the risk of fluid retention and the baseline severity of heart failure.

P1686 Significant mortality benefit of prior beta-blocker use in diabetic patients undergoing coronary intervention

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Background: Studies have shown beta-blockers (BB) to be one of the best classes of drugs to treat coronary artery disease. However, physicians traditionally have avoided prescribing BB for people with diabetes primarily because these drugs can "mask" the warning signs of low blood sugar. Whether prior BB use may be beneficial in diabetic patients undergoing percutaneous coronary intervention (PCI) remains undetermined.
Methods: Study samples consisted of 18,309 consecutive coronary interventions (PCI) performed between July 1997 and February 2001 in a consortium of 8 hospitals. Of the 18,309 patients who underwent PCI, 4,856 were diabetics. In the diabetic cohort, 1,772 had insulin dependent (IDDM) and 3,084 patients had non insulin-dependent (NIDDM). Clinical, procedure, and outcome data were collected prospectively by use of a standardized data collection form agreed on by the participating centers.
Results: There was significant reduction in unadjusted peri-procedural mortality rates in diabetic patients receiving beta-blockers (table). After adjustment for demographics and comorbidities, prior beta-blocker use was associated with a significant survival benefit in IDDM with adjusted odds ratio of 0.49 (95% CI: 0.25 - 0.97, p=0.03) and no significant difference in NIDDM with odds ratio of 0.75 (95% CI: 0.38-1.49, p=0.42).

	IDDM (no BB) n=580	IBBM + BB n=1192	NIDDM (no BB) n=887	NIDDM + BB n=2197
Death	4.48%	2.35%	2.82%	1.32%
MI	0.69%	3.36%	2.37%	2.05%
Stroke	0.52%	0.25%	0.23%	0.36%
Emergent CABG	0.86%	1.01%	0.79%	0.68%
Death/MI/stroke/CABG	6.38%	6.46%	5.64%	3.73%

Effect of prior beta-blocker (BB) use in diabetis undergoing percutaneous coronary intervention. Diabetic status is stratified by insulin dependent (IDDM) and non insulin dependent (NIDDM)

Conclusions: In this cohort of diabetics undergoing PCI use of beta-blockers was associated with significantly improved peri-procedural survival. A logistic regression model suggests significantly improved risk-adjusted survival with prior beta-blocker use in IDDM patients.

P1687 Lack of benefit of intravenous GP IIb/IIIa inhibitors in diabetic patients undergoing percutaneous coronary intervention is explained by differences in baseline characteristics

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Background: There has been conflicting evidence in the literature regarding effect of IIb/IIIa inhibitors in diabetic patients with coronary artery disease. The EPISTENT trial showed significant benefit in diabetic patients receiving IIb/IIIa inhibitors whereas the ASSENT-3 study showed worse outcome in diabetics with these agents. We systematically analyzed clinical outcomes in consecutive diabetic patients undergoing percutaneous coronary intervention (PCI) stratified by glycoprotein IIb/IIIa use.
Methods: Study samples consisted of 18,309 consecutive PCI performed between July 1997 and February 2001 in a consortium of 8 hospitals. Of the 18,309 patients who underwent PCI, 4856 were diabetics. In the diabetic cohort, 1,772 had IDDM and 3,084 patients had NIDDM. Clinical, procedure, and outcome data were collected prospectively by use of a standardized data collection form agreed on by the participating centers.
Results: Mortality and the composite of death/MI/stroke/emergent CABG occurred significantly more often in diabetic patients receiving IIb/IIIa inhibitors. After adjustment for demographics and comorbidities, the adjusted odds ratios of death with IIb/IIIa vs no-IIb/IIIa in IDDM (OR 1.9, 95% CI 0.9-3.7, p=0.06) and NIDDM (OR 1.03, 95% CI 0.5-2.0, p=0.91) patients were not significantly different.

	IDDM (no IIb/IIIa) n=1050	IDDM+IIb/IIIa n=722	NIDDM (no IIb/IIIa) n=1719	NIDDM+IIb/IIIa n=1365
Death	2.19%	4.29%	1.51%	2.05%
MI	1.71%	3.60%	1.69%	2.71%
Stroke	0.29%	0.42%	0.06%	0.66%
Emergent CABG	1.14%	0.69%	0.76%	066%
Death/MI/Stroke/CABG	5.05%	8.45%	3.72%	4.98%

Clinical outcomes of diabetic patients undergoing percutaneous intervention stratified by glycoprotein IIb/IIIa use

Conclusions: In this cohort of diabetics undergoing PCI use of IIb/IIIa inhibitors was associated with worse outcomes particularly in patients with IDDM. Multivariate analyses revealed that the adverse clinical outcomes were explained by differences in prevalent and incident disease characteristics between diabetics and non-diabetics.

P1688 Pregnancy induced changes in type I diabetic women

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Background: Pregnancy induces changes in blood volume and cardiac output. Aim of the following study was to investigate the course of hemodynamic parameters under the increased volume load during pregnancy and delivery in women with insulin dependent diabetes mellitus (IDDM).
Methods: Therefore we examined 34 pregnant women with IDDM. The control group (C) consists of 23 healthy pregnant women. All women underwent echocardiography at the 8th, 12th, 24th, 32th week of gestation and postpartum. Using M-mode echocardiography morphological parameters (left ventricular(LV) mass index) and systolic function (fractional shortening FS; %) were determined. The parameters of LV diastolic function were assessed by Doppler-echocardiographic analysis of the diastolic transmitral flow: the maximal early (VE) and late velocity of diastolic filling; the E/A-ratio; the deceleration time (DT) and the isovolumetric relaxation time(IVRT).
Results: In all women an increase of LVMMI (60±2 vs 69±3 g/m^2; p=n.s.), a decrease of FS (35 vs 28%) and diastolic dysfunction was documented. In C a delayed relaxation pattern (VE: 0.54±0.05 m/s; E/A: 0.8±0.2, DT: 241±11 ms; IVRT: 129±8 ms) at the 32th week of gestation was found. 16 diabetics already showed these signs at the beginning of pregnancy. From midpregnancy these women developed a restrictive diastolic filling pattern (VE: 1.1±0.07 m/s; E/A: 2.1±0.1; DT: 123±8 ms; IVRT: 62±2 ms). The remaining 8 diabetics had a comparable restrictive filling pattern during vaginal delivery. There were no complications in C. In women with IDDM 1 maternal and 2 fetal deaths occurred during labor/delivery and 7 women suffered from ventricular arrhythmias ($p < 0.001$). All changes induced by pregnancy were reversible in C within days, but persisted over weeks in diabetics.
Thus: In healthy women pregnancy induces a reversible physiologic LV hypertrophy, a delayed relaxation pattern and a temporarly decrease of FS. Pregnant women with IDDM developed signs of restriction and had a markedly increased risk of maternal and fetal mortality.

P1689 Myocardial perfusion and function in type 1 diabetic patients

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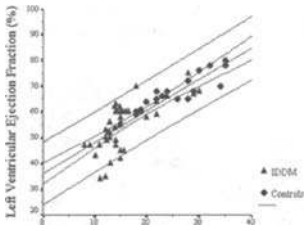
To investigate the relationship among myocardial perfusion and function, and circulating levels of inflammatory cytokines in young adult patients with IDDM. Twenty two patients (BMI 23±2 kg/m^2; age 32±8.3 years) without macro- or microvascular complications and arterial hypertension, and 10 healthy subjects (controls: BMI 24±2 kg/m^2; age 31±3 years) were studied. LV dimensions (LVEDVI) and function (LVEF) were measured by 2D echocardiography; myocardial perfusion (myocardial peak intensity, MPI) was assessed with contrast echocardiography at rest and during handgrip. Patients and controls had similar baseline values for LVEDVI and LVEF. Patients were classified into two groups on the basis of LV response to handgrip: group A-LVEF decline of >0.05 units, group B-LVEF increase or no change. Baseline (14.2±1 and 16.6±3.8 vs 20.5±2.2 gray scales; pA<0.001, and pB<0.05) and peak handgrip values for MPI (12.8±1.6 and 21.3±7.9 vs 30.7±3.3 gray scales; pA<0.001, pB<0.05) were significantly lower in diabetic patients as compared to controls. Among patients, group B had higher values of MPI both at rest (p<0.05) and at peak handgrip (p=0.008). Considering both baseline and peak handgrip values in patients and controls (n=64), a strong correlation between MPI and LVEF was seen (r=0.828, p<0.0001, Figure 1).



In diabetic patients plasma levels of TNF-alfa (8.5±1.2 vs 1.1±1.0 pg/ml, p<0.001) and IL-6 (2.5±0.3 vs 0.7±0.2 pg/ml, p<0.01) were significantly higher than in controls. Myocardial perfusion is impaired in young IDDM patients without micro- and macrovascular complications. This abnormality is strongly related to myocardial function and conditioned LV performance during isometric exercise, and is associated with high plasma levels of TNF-alfa and IL-6.

P1690 Prognostic value of dobutamine-atropine stress myocardial perfusion imaging in patients with diabetes mellitus

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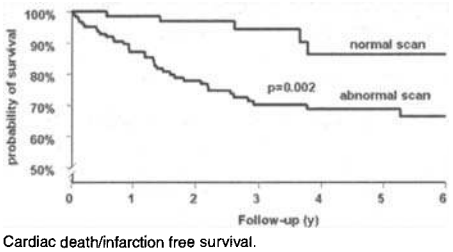
Objective: Exercise tolerance in patients with diabetes mellitus is frequently impaired due to non-cardiac disease, as claudication and polyneuropathy. This study assesses the prognostic value of dobutamine stress myocardial perfusion imaging in patients with diabetes mellitus.

Methods: A total of 207 consecutive diabetic patients unable to perform an exercise test underwent dobutamine-atropine stress myocardial perfusion imaging. Follow-up was successful in 206 of 207 (99.5%) patients. Twelve patients underwent early (<60 days) revascularization and were excluded from the analysis. End points during follow up were hard cardiac events defined as cardiac death and non-fatal myocardial infarction.

Results: Abnormal myocardial perfusion was detected in 125 (64%) patients. During 4.1±2.4 year follow-up, 73 (38%) deaths occurred of which 36 (49%) were due to cardiac causes. Nonfatal myocardial infarction occurred in 7 (4%) patients and 45 (23%) patients underwent late coronary revascularization. Cardiac death occurred in 2 of 69 (3%) patients with normal myocardial perfusion and in 34 of 125 (27%) patients with perfusion abnormalities (P<0.0001). A multivariable Cox proportional-hazards model demonstrated that the presence of an abnormal scan had an incremental prognostic value for the prediction of cardiac death (hazard ratio = 7.5, 95%CI 1.8-32), additional to clinical and stress test data. The summed stress score (SSS) was an important predictor of cardiac death, with a hazard ratio of 1.2 (95%CI 1.07-1.34) per 1 unit increment.

Conclusions: Dobutamine-atropine stress myocardial perfusion imaging provides prognostic information incremental to clinical data in patients with diabetes mellitus unable to perform an exercise stress test.



Cardiac death/infarction free survival.

P1691 Prognostic value of dobutamine stress echocardiography in patients with diabetes mellitus

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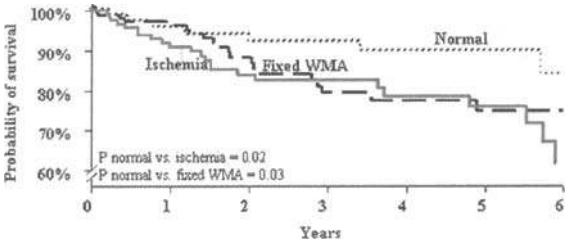
Purpose: The aim of this study was to assess the incremental value of dobutamine stress echocardiography (DSE) for the risk stratification of diabetic patients.

Background: Exercise capacity is frequently impaired in patients with diabetes mellitus. The role of DSE in the risk stratification of diabetic patients has not been well defined.

Patients and methods: We studied 396 diabetic patients [mean age 61±11 years, 252 men (64%)] who underwent DSE for evaluation of known or suspected coronary artery disease. Endpoints were hard cardiac events (cardiac death and nonfatal myocardial infarction) and all causes of mortality.

Results: During a median follow up of 3 years, 97 patients (24%) died (55 cardiac deaths) and 27 patients had nonfatal myocardial infarction. Curves for survival free of hard cardiac events in patients with normal DSE, ischemia and fixed wall motion abnormalities (WMA) are presented in the picture below: P value between normal DSE and ischemia was 0,02; P value between normal DSE and fixed WMA was 0,03. In an incremental multivariate analysis model, clinical predictors of hard cardiac events were history of congestive heart failure and previous myocardial infarction. The percentage of ischemic segments was incremental to the clinical model in the prediction of hard cardiac events (chi square 37 vs. 18, p<0,05). Clinical predictors of all causes of mortality were history of congestive heart failure, age and hypercholesterolemia. Wall motion score index at peak stress was incremental to the clinical model in the prediction of mortality (chi square = 47 vs. 33, p<0,05).



Survival curves for hard cardiac events.

Conclusions: DSE provides incremental data for the prediction of mortality and hard cardiac events in patients with diabetes mellitus.

P1692 Detection and treatment of silent myocardial ischaemia in high risk diabetic patients decrease the occurrence of major cardiac events

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Background: Because silent myocardial ischemia (SMI) has been demonstrated to be harmful in diabetic patients, recent guidelines recommend detection of SMI in high risk asymptomatic subjects. The impact of treatments in such patients however has not been fully established. Accordingly, we aimed to determine the ability of an ischemia guided strategy to decrease the occurrence of major cardiac adverse events (MACEs = cardiac death + non fatal myocardial infarction (MI) in high risk asymptomatic diabetic patients.
Methods: This monocenter prospective study compared the occurrence of MACEs in 2 groups of asymptomatic diabetic patients presenting with 2 or more associated risk factors, and/or proteinuria, and/or peripheral vascular disease. Each patient underwent an exercise or dipyridamole thallium 201 perfusion scan for detection of SMI. Group I consisted in a population of 204 patients prospectively included between 1991 and 1995, in which therapeutic measures were left at the discretion of the referral physician. Group II (n = 166 patients included between 1997 and 2000) underwent predifined systematic medical treatments and/or revascularisation: statins if LDLc > 130 mg/dl, ACE inhibitors for high blood pressure, beta-blockers and aspirin in case of abnormal perfusion scan, and invasive strategy (coronary angiography and revascularisation when suitable) in case of perfusion defect involving > 15% of left ventricle. Follow-up was similar for both group (24±12 vs 22±8 months).
Results: Baseline data were similar in Group I and II: men 86 vs 85%, age 59±11 vs 58±12 yrs, body mass index 28.7±5.6 vs 29.0±5.3, type II diabetes 76 vs 81%, duration of diabetes 14±8 vs 12±9 yrs, and mean number of risk factors 3.9±1.5 vs 4.2±2.0 respectively, NS for all. Proteinuria however was more frequent in group I (58 vs 43%, p=0.06).
MACEs occurred more frequently in group I than in group II: n=29 - 14.2% vs n=10 - 6.1% - Odd ratio 2.4 [1.2-4.1], p <0.01. This decrease in MACEs in group II was related to a lower occurrence of MI (n=19 - 9.3% vs n=3 - 1.8%, p<0.05), without significant decrease in cardiac death (n=10 - 4.9% vs n=7 - 4.2%, NS). After adjustment for baseline variables, the 2 independent predictors of future MACEs were an aged > 65 yrs (p=0.04) and belonging to group I (p=0.04).
Conclusion: Detection and aggressive treatments of SMI in high risk diabetic patients is efficient for decreasing MACEs and non fatal MI in the present study. Larger studies are needed to assess the impact of such risk reduction strategies on mortality.

P1693 The effect of diabetes on plasma potassium concentrations in acute coronary syndromes

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Objectives: To compare plasma potassium concentrations in diabetic and non-diabetic patients with acute coronary syndromes (ACS).
Background: Acute phase hypokalaemia in ACS occurs in response to adrenergic activation which stimulates membrane bound sodium-potassium-ATPase and drives potassium into the cells. It is not known if the hypokalaemia is attenuated in patients with diabetes, due to the high prevalence of sympathetic nerve dysfunction.
Methods: Prospective cohort study of 1783 patients presenting with ACS. Patients were stratified by duration of chest pain, diabetic status and pretreatment with beta-blockers.
Results: In patients presenting within 6 hours of symptom onset, there was a progressive increase in plasma potassium concentrations from 4.08±0.47 mmol/l in patients presenting within 2 hours (n=438), through 4.18±0.47 mmol/l in patients presenting between 2 and 4 hours (n=237), to 4.25 ±0.56 mmol/l in patients presenting between 4 and 6 hours (n=122, p=0.0007). This pattern of increasing plasma potassium concentration with duration of chest pain was not seen in patients pretreated with beta-blockers or in patients with diabetes in whom potassium concentrations were significantly higher than in patients without diabetes (4.3±0.53 versus 4.1±0.46, p<0.0001). Multivariate analysis identified diabetes as a predictor of a plasma potassium concentration in the upper half of the distribution (OR 1.69; CI 1.34-2.13), independently of renal dysfunction, ACE-inhibition, diuretic therapy and a range of other baseline variables. Acute phase ventricular arrhythmias during the first 6 hours were recorded less frequently in patients with than without diabetes (3.7% versus 8.6%, p=0.02).
Conclusion: Relative insulin deficiency almost certainly accounted for the increased plasma potassium concentrations in diabetic patients with ACS, but the absence of an early potassium dip in this group was also seen in patients on beta-blockers and is more plausibly attributed to sympathetic nerve dysfunction. This may be beneficial if it helps protect diabetic patients against acute phase ventricular arrhythmias.

P1694 Diabetic patients after percutaneous interventions in native coronary arteries: gender differences in clinical outcomes at 1-year follow-up

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Background: We assessed whether female gender is a risk factor for clinical events at 1-year follow-up in diabetic patients undergoing percutaneous coronary interventions (PCI).
Methods: Among 1832 consecutive diabetic patients who underwent 2291 PCIs in native coronary vessels, 716 pts (39%) were women. Pts with acute MI within 72h before PCI or pts with vein graft PCI were excluded.
Results: Women were older (66±11 yrs vs. 64±10 yrs, P<.0001) and had less prior MI (50% vs. 55%, P=.047) and prior CABG (29% vs. 35%, P<.0019) than men. Chronic renal insufficiency (CRI, 14% vs. 12%, P=.152) and peripheral vascular disease (PVD, 28% vs. 25%,P=.108) were similar in the two groups. Multivessel PCI occurred in 26% of both genders (P=.796). In-hospital, women had higher rates of (i) acute renal failure (8% vs. 4%, p<.0001),(ii) non-Q-wave MI (14% vs. 10%, P=.014),(iii) major vascular complication (8% vs. 3%, P<.0001) and (iv) blood transfusion (12% vs. 3%, P.<0001). In-hospital mortality (1.7% vs. 1.0%, P=0.163) repeat PCI (3% vs. 2%, P=0.106), CABG (2% vs 2%, P=.517) and stroke (0.2% vs. 0.1% P=.565) were similar in the two groups. At 1-year follow-up, mortality was higher in women than in men (11.3% vs. 7.7%, P=.0063). Multivariate predictors of 1-year mortality included age (OR=1.06, P<.0001), CRI (OR=3.67, P<.0.0001), prior CABG (OR=1.85, P=.0002) and PVD (OR=2.13, P<.0001), but not female gender. Other clinical events were similar at 1-year (table).

Results @ 1-year follow-up

	Female	Male	P value
Death (%)	11.3	7.7	0.006
Q-wave-MI (%)	1.9	1.2	0.216
CABG (%)	7.4	8.2	0.563
PCI (%)	16.6	16.4	0.893
MACE	33.2	31.5	0.407

CABG = Coronary artery bypass grafting; MACE=Death; MI; Target vessel revascularization

Conclusions: In diabetics undergoing PCI, women have more in-hospital bleeding and major vascular complications, but similar in-hospital ischemic complications compared to men. At 1-year, total mortality is higher in women, but this finding appears to be related to older age and comorbid conditions of women rather than female gender.

P1695 Spectral analysis of heart rate variability during orthostatic load: improvement in diagnostics of cardiovascular diabetic autonomic neuropathy?

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Aim: To improve sensitivity of short-term spectral analysis of heart rate variability (SA-HRV) in assessment of autonomic dysfunction in diabetes.
Methods: Comparison of results of short-term time- and frequency-domain analysis of HRV as obtained by system VariaCardio TF4® during single positions and during modified orthostatic load (supine1-standing-supine2, each position 300 seconds) in diabetic patients with excellent metabolic control (n=80, age 39.2±12.9, diabetes duration 16.4±10.4 years, HbA1c =146±21% of mean reference range), and in non-diabetic controls (n=150, age 40.6±13.2 years). A standard reflex tests battery as proposed by Ewing [Ewing et al, 1985] was performed for excluding cardiovascular autonomic neuropathy (CAN) in diabetic subjects. Coronary artery disease was excluded clinically.
Results: None of short-term frequency-domain parameters (absolute and logarithmic (LN) values of spectral powers in total (TF), low- (LF) and high-frequency (HF) bands and its centroid frequencies) obtained in single "supine" or "standing" positions revealed a significant difference between well-controlled patients and healthy controls (p>0.3). However, during modified orthostatic load, significant differences in Delta LN TF(supine1-supine2) and in Delta LN LF(supine1-supine2) values between diabetic and healthy subjects were recorded (-0.3 vs. -0.2 LN(ms2), p=0.05 and -0.4 vs. 0.1 LN(ms2), p=0.001, resp.) along with no significant intergroup differences in related centroid frequencies, which suggests a delayed recovery of LF spectral power in well-controlled diabetic subjects after active orthostatic manipulation.
Conclusions: When compared with single position measurements, the modified orthostatic load seems to improve the sensitivity of SA-HRV examination. In well-controlled diabetic subjects without CAN, the delayed recovery of LF band spectral power after active orthostatic manipulation might represent an early warning sign of autonomic dysfunction.

P1696 Evidence of decreased left ventricular longitudinal contraction despite normal ejection fraction in patients with type 2 diabetes mellitus

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Left ventricular diastolic dysfunction may be a very early abnormality in type 2 diabetes. New echocardiographic techniques, including color M-mode and Doppler tissue tracking seems to improve the detection of the pseudonormal diastolic filling pattern and analysis of the longitudinal myocardial performance of the left ventricle. The aim of the present study was to evaluate left ventricular systolic and diastolic function in patients with type 2 diabetes without complications using these echocardiographic methods.

We examined 32 patients with type 2 diabetes mellitus. Average age was 52.7 years (39-72 years). Mean diabetes duration was 4 years (0.5- 20 years). Thirty age and sex matched normal subjects served as controls.

Exclusion criteria's were blood pressure > 130/85 mmHg, ejection fraction < 55%, history of cardiac disease, abnormal ECG, valvulopathy, albuminuria above 20 mg/l or presence of any other diabetes related complication.

Left ventricular systolic function was evaluated by fractional shortening and ejection fraction obtained by Simpson's disc-summation method, using second harmonic imaging. Diastolic function was evaluated by combined analysis of mitral inflow and color M-mode flow propagation. To assess longitudinal myocardial performance of the left ventricle, tissue tracking imaging was performed and presented as a 16 segments tissue tracking wall-motion-score.

Mean ejection fraction was 64%. Diastolic dysfunction was present in 15 patients with 16 patients exhibiting impaired relaxation pattern and 9 patients with pseudonormal filling pattern. Patients with diabetes had significantly lower tissue tracking score compared to normal subjects (6.0 ± 1.5 mm vs 7.6 ± 1.5 mm)($p<0.01$). Patients with diastolic dysfunction had a more profound reduction in tissue tracking score compared to patients without diastolic dysfunction (5.6 ± 1.3 mm vs 6.7 ± 1.5 mm) ($p<0.05$). Results were not correlated to BMI, HbA1c, blood pressure or type of antidiabetic therapy.

In conclusion, decreased longitudinal contraction of the left ventricle was found in normotensive patients with type 2 diabetes, indicating the presence of abnormal systolic function, which is not detected by conventional 2D echocardiography.

P1697 Effect of diabetes on major determinants of myocardial oxygen demand in acute coronary syndromes

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Objectives To determine whether major determinants of myocardial oxygen demand (heart rate and blood pressure) are increased in diabetic patients with acute coronary syndromes.

Background Contractile dysfunction remote from the myocardium at risk may contribute to the poor outcome in diabetic patients with acute coronary syndromes. This in turn may reflect problems with oxygen delivery due to severe coronary artery disease but it is not known if oxygen demand is also affected.

Methods Prospective cohort study of 1783 patients with acute coronary syndromes. The presenting heart rate and blood pressure were compared in diabetic (n=483) and nondiabetic (n=1300) subgroups.

Results Rates of heart failure were higher (18.9% versus 12.4%, p=0.0009) in diabetic than nondiabetic patients. Major haemodynamic determinants of myocardial oxygen demand were also higher in diabetic patients: heart rate 82±20 versus 77±19 beats/minute (p=0.0002); systolic blood pressure 148±30 versus 143±29 mmHg (p=0.0005); rate-pressure product 12321±4160 versus 11121±3820 beats/minute.mmHg ($p<0.0001$). Logistic regression analysis confirmed diabetes as a significant determinant of presenting heart rate (OR 1.62; CI 1.23-2.14), systolic blood pressure (OR 1.28; CI 1.03-1.60) and rate pressure product (OR 1.65; CI 1.25-2.18). These effects of diabetes were independent of multiple baseline variables including: previous acute coronary syndromes, presentation with unstable angina or myocardial infarction, heart failure, and drug therapy.

Conclusions In diabetic patients with acute coronary syndromes, heart failure is more common and major determinants of myocardial oxygen demand are increased compared with nondiabetic patients. The increase in oxygen demand is independent of heart failure and multiple other baseline variables. It provides a potential contributory mechanism of exaggerated regional ischaemia and propensity to heart failure in this high risk group.

P1698 Coronary artery disease progression in diabetics compared to non diabetics

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Background: Diabetes mellitus is a strong risk factor for coronary artery disease (CAD). However, the progression over time of CAD in diabetic patients has never been compared to non diabetics.

Methods: The progression of CAD in 23 consecutive diabetics was compared to 36 age-matched (mean age 65 y.o. in both groups) non diabetics undergoing 2 coronary angiograms with a delay of more than 3 years between both exams (mean 4.75 y. - 3 to 7 y. in both groups). Patients with a history of CABG were excluded. Coronary angiographies were independently analysed by two experimented observers. For each arterial segment, the severity of stenosis and the length of the diseased segment were analysed (visual quantification). Stenosis treated by coronary angioplasty were excluded from the analysis. The analysis was also conducted separately on proximal (left main, LAD 1 and 2, circumflex 1, 2 and 3 when dominant and RCA 1, 2 and 3 when dominant) and distal (other coronary segments) coronary bed.

Results: Other coronary risk factors were similar in diabetics and non diabetics. At the first coronary angiogram, diabetics had a higher rate of significant (>50%) stenosis compared to non diabetics (2.29 ± 1.33 stenosis/patient vs. 1.47 ± 1.54 respectively, mean ± SEM, $p<0.05$). The second coronary angiogram demonstrated a higher rate of significant stenosis in diabetics compared to non-diabetics (4.79 ± 1.52 stenosis/patient vs. 3.34 ± 2.11 respectively, $p<0.05$). Compared to the first exam, CAD progression on the second exam was mainly due to an increase of the rate of stenosis on distal arteries in diabetics compared to non diabetics (0.71 ± 0.70 stenosis/patient vs. 0.44 ± 0.76 respectively at the first exam and 2.36 ± 1.29 vs. 1.34 ± 1.30 at the second exam respectively $p<0.05$ - corresponding to an increase of 0.35 stenosis/y. in diabetics vs. 0.19 stenosis/y. in non diabetics, $p<0.05$). The progression of CAD on proximal segments was similar in diabetics and non diabetics (1.57 ± 1.18 stenosis/patient vs. 1.03 ± 0.03 respectively at the first exam and 2.42 ± 1.29 vs. 2.00 ± 1.26 respectively at the second exam $p<0.05$ - corresponding to an increase of 0.18 stenosis/y. vs. 0.20 stenosis/y. respectively, p=NS). Similar results were found considering the length of diseased segments.

Conclusion: The progression of CAD appears to be more rapid on distal branches in diabetics compared to non diabetics. This result must be taken into consideration when a decision of revascularisation is discussed in diabetic patients.

NUTRITION, ALCOHOL AND CARDIOVASCULAR RISK

P1699 Daily intake of red wine inhibits mural thrombosis, platelet Rho-A membrane protein translocation and monocyte tissue factor mRNA expression

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Moderate consumption of red wine has been associated to a reduction in cardiovascular diseases, but the mechanisms are not fully understood.
Objectives: We have studied whether the protective effects of dietary red wine (local variety of Tempranillo, 12.8% alcohol v/v) could be related to inhibition of thrombosis.
Methods: Two groups of animals (A and B) were fed for 100 days an hyperlipidemic diet containing 2% of cholesterol and 20% of saturated fat. Group B also received a daily moderate dose of alcohol (40g alcohol/day) provided by red wine. Thrombosis triggered by vascular injury was evaluated in the previously validated and standardized Badimon perfusion chamber by radioisotopic evaluation of deposited platelets.Blood was collected and platelets isolated by standard methods, processed with homogenate buffer and subfractioned into cytoplasm and membrane proteins that were analyzed by Western Blotting for Rho-A. Peripheral blood monocytes were obtained by elutriation, seeded in culture dishes and activated with LPS (0.1μg/dish). Cell extracts were processed by conventional molecular biology techniques to obtain mRNA. TF mRNA and a control GAPDH mRNA were coamplified in a semiquantitative RT-PCR analysis.
Results: Mural platelet deposition was significantly reduced both on severely (56±10 vs 30±6 PLT*106/cm^2, $p<0.05$, for Groups A and B respectively) and mildly (8±1 vs 5±0.8 PLT*106/cm^2, $p<0.05$, Groups A and B respectively) damaged vessel wall in wine-fed animals. Expression of Rho-A in the platelet membrane (active form) was reduced in wine-fed animals while the cytoplasmatic Rho-A expression (inactive form) increased. Aditionally, TFmRNA expression in LPS stimulated monocytes was reduced in Group B. Total cholesterol levels were not significantly different between both groups.
Conclusions: Moderate red wine intake significantly reduces platelet deposition triggered by damaged vessel wall. This inhibitory effect is evident at all levels of vascular damage indicating a general passivation effect of the thrombotic response to injury. Wine intake inhibits Rho-A translocation to the platelet membrane. Rho-A, a small G-protein, needs to be localized in the membrane to be active for biological actions, a major one being the regulation of cellular cytoskeleton assembly and shape change. Peripheral blood monocytes of animals ingesting wine have a lower capacity to induce TF mRNA expression. Hence a daily moderate intake of wine inhibits different pathways that converge in a reduced thrombotic risk.

P1700 Moderate alcohol consumption is associated with slower progression of coronary atherosclerosis in middle aged women with CAD – FemCorRisk study

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Background: Moderate alcohol intake is associated with lower risk of coronary heart disease and related to reduced mortality after acute myocardial infarction. However, to our knowledge, no previous study has examined the effect of alcohol on human coronary arteries with serial computer-assisted quantitative coronary angiography (QCA) which provides a reliable approach to investigate the progression of coronary atherosclerosis in vivo.
Aim: to investigate the relationship between alcohol consumption and the progression of coronary artery disease in terms of repeated quantitative coronary angiography in middle aged women with coronary heart disease.
Method: The Stockholm Female Coronary Risk (FemCorRisk) study consisted of 292 women patients (age 56±7) who were hospitalized for acute coronary events, 110 for acute myocardial infarction and 182 for unstable angina. Computer-assisted coronary angiography was performed within 3 to 6 months of the visit to the research clinic and 3 years and 3 months (range between 2 to 5 years) later, on 106 patients. QCA measurements were carried out primarily because the patients were participants in the FemCorRisk study. Alcohol consumption was assessed by a standard measure of frequency and quantity, and alcohol intake (gram per day) was calculated on the basis of the known alcohol content of beverages.
Results: Ninety-six patients had valid alcohol data and repeated QCA measurements (mean alcohol consumption 4.18±6.95 g/day). Patients consuming over 5g/day of alcohol (N=58) had significantly lower mean segment diameter progression then the abstainers (N=14) and patients between 0-5 g/day (N=24): -0.011±0.031 mm versus 0.127±0.044 mm and 0.134±0,021 mm, respectively (p=.0005). The results remained essentially the same after adjusting for age, event of inclusion to the study, smoking, educational status, history of diabetes mellitus, sedentary lifestyle, BMI, history of hyperlipidemia, triglycerides, HDL, fibrinogen, history of hypertension and menopausal status.
Conclusion: in middle aged women with coronary heart disease moderate alcohol consumption showed an inverse association with the progression of coronary atherosclerosis independently of well-established clinical markers.

P1701 Genetic variation in alcohol dehydrogenase and effect of alcohol consumption on C-reactive protein in a large population-based study

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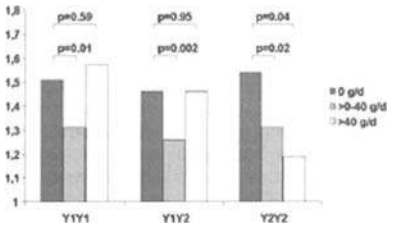
Background: A polymorphism in the gene for alcohol dehydrogenase type 3 (ADH3) alters the rate of alcohol metabolism. Recently, it has been reported that this polymorphism might modify the beneficial effects of moderate alcohol consumption on coronary events. A strong association between C-reactive protein (CRP) and coronary events has been frequently reported. We investigated the effect of alcohol consumption on levels of CRP and its relation to the ADH3-polymorphism.
Methods: A subsample of 3650 men and women aged 25-74 years of the third MONICA-Augsburg survey (1994/95) was studied. CRP was measured by high-sensitive IRMA (range 0.05-10.0 mg/L), the ADH3-polymorphism was determined by polymerase chain reaction and subsequent MALDI-TOFF analysis. Differences of geometric mean levels of CRP adjusted for age, gender, smoking status, BMI, Hdl-cholesterol, education, and physical activity were calculated between categories of alcohol intake (0 g/day = reference).



Results: A U-shaped relation between daily alcohol intake and adjusted geometric mean levels of CRP was seen in the whole sample. However, homozygosity for the Y22 allel was associated with the largest decreased CRP levels (figure). Thus, slow metabolizers showed the most pronounced decrease of CRP levels.
Conclusion: These findings might contribute to explain the beneficial effects of moderate alcohol intake on cardiovascular mortality.

P1702 Effect of alcohol intake on C-reactive protein: Consistent Results from three different geographical areas

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Alcohol intake is associated in a U-shaped manner with risk of CHD. The aim of the present study was to confirm and extend the recently reported antiinflammatory effects of moderate alcohol intake.
We investigated the relationship between alcohol intake and C-reactive protein (CRP) in population-based cross-sectional samples of three European communities, in Germany, the UK, and in France (MONICA Augsburg 1994/95, 2275 men and 2186 women, 25-74 years; Glasgow MONICA 1994/95, 525/597, 25-74 years, and MONICA Lille 1994/95, 581/574, 35-64 years). Alcohol intake was collected by standardized interview and CRP determined by IRMA (range 0.05-10 mg/L). Geometric means of CRP were calculated among categories of alcohol intake by general linear regression after adjustment for several potential confounders including age, gender, smoking status, body-mass-index, HDL-cholesterol, education, and physical activity for each sample.
We were able to confirm the reported U-shaped relationship between alcohol intake and CRP in three independent, random samples of the general population (table). The amount of alcohol consumed a day associated with the lowest CRP levels differed between samples and between men and women.

Alcohol g/d	0	>0-20	>20-40	>40-60	>60-80	>80	p*	p#
Augsburg	1.52	1.36	1.37	1.46	1.66	1.65	0.17	0.04
Glasgow	1.54	1.28	1.49	1.31	1.55	1.69	0.14	0.35
Lille	1.62	1.33	1.29	1.55	1.61	1.92	0.53	0.11

Geometric Means of CRP by Alcohol Intake: adjusted for age, sex, smoking status, BMI, HDL, physical activity, education.p* for linear term, p# for quadratic term

Conclusion: Non-drinkers and heavy drinkers had higher CRP levels than moderate drinkers in representative population-based samples. Since CRP represents an CHD risk factor, this association might represent a link between moderate alcohol intake and reduced CHD mortality.

P1703 Mediterranean diet: an "ecological" paradox or inverse association with clinical and biochemical markers related to cardiovascular risk

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Background: Many investigators based on the results from the Seven Countries study and the Lyon Heart Study have recognized the beneficial role of the Mediterranean diet in cardiovascular diseases. The aim of this work is to evaluate the effect of the Mediterranean-type of diet on several clinical and biochemical markers, associated to CVD risk.

Methods: The ATTICA study is a prospective population -based cohort designed to enroll 3073 men and women from the greater area of Athens. A random algorithm was developed and stratified, by sex- age; sampling was performed, during 2001. In this work data from 654 men (18-87 years old) and 826 women (18-89 years old) were analysed. The consumption of red meat, chicken, fishes, vegetables, legumes, pasta, salads, cereals, diary products, sweets and fruits was investigated as an average per week, during the past year, using a special nutritional questionnaire, developed by the National School of Public Health. We defined subjects who adopt this type of diet using as cut-off points the median values of the monthly food consumption score.

Results: 583 (39%) of the subjects were defined closer to the Mediterranean diet. The adoption of Mediterranean diet is associated with a reduction of total cholesterol (212±25 vs. 217 ±38 mg/dl, P<0.05), triglycerides (112±17 vs. 127 ±19 mg/dl, P<0.01), blood glucose concentration (90±8 vs. 94 ±12 mg/dl, P<0.01), fibrinogen (312±33 vs. 328± 31 mg/dl, P<0.05), homocysteine (12±3 vs. 14±5 mg/dl, P<0.05) and systolic blood pressure (122 ± 12 vs. 126 ± 8 mmHg, P<0.05). On the other hand, diet increases HDL-cholesterol (50 ± 5 vs. 47 ± 6 mg/dl, P<0.01) and apoA1 (156±22 vs. 149±24 mg/dl, P<0.01). No associations were found between the adoption of Mediterranean diet and Lp(a), apoB, uric acid, social status (described by educational and financial level), age and sex (P>0.700).

Conclusion: Despite the "ecological" paradox regarding low CVD mortality in Mediterranean populations, where Keys and his colleagues reported at the early 1970s, the protective effect of this traditional diet on atherosclerosis seems to be explained, mainly, due to the modification of several biochemical and clinical markers.

P1704 Moderate alcohol consumption, C-reactive protein and long-term prognosis following successful coronary stenting

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Background: It is well established that moderate alcohol consumption is associated with better long-term prognosis in patients with coronary artery disease. However, the underlying pathophysiologic mechanism is not well known. Moreover, several studies have shown the fundamental role of inflammation in the pathophysiology and outcome of coronary artery disease.We evaluated the influnce of the moderate alcohol consumption (red wine) on the long term prognosis according to the baseline CRP values in patients enrolled in GENERATION study.

Methods: The GENERATION study was designed to evaluate globally, the impact of several serum markets estimated upon admittance (CRP, Lpa, homocystein and seropositivity for chlamydial infection) on the long-term cardiovascular morbidity and mortality as well as on the restenosis rate after successful coronary stenting (CS). For the purpose of this study a total of 483 consecutive patients treated for stable or unstable coronary syndromes, were recruited in a period of 28 months in our institute. Complete clinical follow up was obtained from 465 (96.3%) pts for a period of 3-years. Information concerning alcohol consumption (red wine) was prospectively collected.

Results: Out of 166 (166/465; 35.7%) patiens have reported moderate alcohol consumtion during the follow-up. By 3-year the incidence of the composite endpoint of cardiac death new myocardial infarction and rehospitalization for unstable angina was 16.3%. Patients with a baseline plasma CRP value <0.68mg/dl (defined by ROC analysis) did not show any benefit in the composite endpoint from moderate alcohol consumption (8% among alcohol consumers vs. 7.3% among those who did not drink; p=0.8). However, patient with a plasma CRP >=0.68mg/dl got the greater benefit from moderate alcohol consumption (22.7% among alcohol consumers vs. 40.4% among those who did not drink; p=0.02)

Conclusions: The results of the present analysis suggest that the beneficial effect of alcohol consumption on the long-term complications following successful CS are strongly asociated to the patients' inflammatory status. An antiinflammatory effect of alcohol could not be excluded. More studies are needed to elucidate this issue.

P1705 Micronutrient deficiency, hyperhomocysteinaemia and subclinical atherosclerosis

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Background: While meta-analysis confirmed a lower mortality from ischaemic heart disease in vegetarians (consuming dairy or egg products) than non-vegetarians, the mortality in vegans (consuming no animal products) was not significantly different, suggesting a possible vascular-protective effect of micronutrient

Methods: To test the hypothesis that micronutrient (folate and vitamin B-12) deficiency in rural northern China predisposes to atherosclerosis, we studied 463 asymptomatic Chinese (354 in rural Shanxi, Yu County and 109 age and gender-matched subjects in Hong Kong). Their mean age was 44.7±1.0 yr; 55.3% were males. Carotid intima-media thickness (surrogate atherosclerosis marker, IMT) was measured by high-resolution ultrasound, using an off-line automatic edge-detection and measurement computer software.

Results: The 2 groups of non-smoker (175 from Yu County and 99 from Hong Kong) were matched for renal function, glucose and body mass index. Blood pressures (SBP, DBP), total fasting homocysteine (tHcy) and IMT were significantly higher (p<0.003) and low density lipoprotein cholesterol (LDL-C), folate and vitamin B-12 were significantly lower (p<0.0001) in Yu County. On multivariate linear analysis, age, systolic blood pressure, tHcy and folate but not LDL-C were significantly correlated with carotid IMT (R=0.59; F-value=20.3; p<0.001). On stepwise backward regression analysis of both current smokers and non-smokers in both sites, tHcy (>12μmol/l; odd ratio=2.0; 95% CI=1.2-3.2; p=0.007), diastolic blood pressure, male gender, age and waist-hip ratio were significantly associated with increased IMT (>0.65mm).

Clinical Parameter of Non-smokers

	Yu County	Hong Kong	p-Value
SBP (mmHg)	122.9±14.7	116.6±13.6	0.003
DBP (mmHg)	0.4±10.6	75.7±9.6	0.002
LDL-C (mmol/l)	2.2±0.8	3.5±0.8	<0.0001
Folate (nmol/l)	15.5±15.3	34.2±14.1	<0.0001
Vit B-12 (pmol/l)	148.5±64.4	310.4±139.5	<0.0001
tHcy (umol/l)	19.0±11.6	9.2±2.4	<0.0001
IMT (mm)	0.62±0.09	0.55±0.1	<0.0001

Conclusion: Micronutrient deficiency is associated with higher blood pressure and homocysteine level, and predisposes to atherosclerosis.

P1706 Specific features of nutrition, arterial blood pressure and blood lipids in the long-livers of the north caucasus

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Of all the long-livers' populations, the highest long-living index (93.2%) has been observed in the rural-areas Balkars. They live in the Southern Russia, the North Caucasus, at an altitude 1.500 to 1.200 metres above sea level, engaged in cattle breeding. As it is generally known, in addition to genetic factors, long-living also depends on traditional nutrition.

Aim: Studies of nutritional features, blood pressure (BP), and blood lipids (BL) in long-livers Balkars.

Methods: Using the standard internationally-accepted WHO-recommended epidemiological methods, nutrition, BP level, BL have been studied in the long-livers, aged 91 to 102 (n = 27) and a random sample of men, aged 40 to 59 (n = 122), i.e. the control group.

Results: Basic sources of protein, fats and carbohydrates in the long-livers' food ration are as follows: lactic acid foods, cheese, yeast-free unleavened bread of maize/wheat flour. Widely taken are honey, numerous wild berries, grasses, featuring probiotic and antihypoxant effect, like lactic acid foods, with no margarine and restricted use of refined sugar.

Tab.1

Variable	Long-Livers	Control group	P-value for difference
n	27	122	
Protein, g/day	122 ± 62.9	93 ± 43.9	0.005
Animal protein, g/day	79 ± 42.6	51 ± 32.2	0.002
Fats, g/day	125 ± 60.4	110 ± 54.0	0.2333
Carbohydrates, g/day	357 ± 148.7	403 ± 193.0	0.2464
Sugar, g/day	40.1 ± 13.0	85 ± 66.7	0.0007
Systolic BP, mm Hg	126.2 ± 6.64	137.6 ± 20.2	0.0044
Diastolic BP, mm Hg	68.0 ± 5.76	88.4 ± 11.3	0.00001
Total cholesterole, mg/dl	175.7 ± 18.4	193.0 ± 48.2	0.069
Triglycererides, mg/dl	54.6 ± 10.23	129.1 ± 91.4	0.0001
HDL cholesterol, mg/dl	40.52 ± 10.1	41.8 ± 12.0	0.6

Long-livers' nutrition with high content of animal protein, lower content of refined sugar is associated with more optimal level of BP and triglyperides (TG). Optimized BP level and blood TG content seems to be in the relation with the use of large quantities of probiotic foods, vegetable origin antioxidants, producing a favourable effect on the intestinal microflora and all kinds of metabolism.

P1707 Validation of a short food questionnaire for assessment of dietary habits

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Background: Dietary changes such as reducing the consumption of foods high in saturated fat and increasing the daily intake of fruits and vegetables can have beneficial effects on long-term health. Necessary for dietary counseling is accurate information on patient's diets. Most methods used to examine an individual's diet (food record, diet interview, food frequency questionnaires)are too complicated and time-consuming in routine clinical use. There is need for a fast tool for food assessment.

Objectives: To evaluate a simple food questionnaire for use in clinical practice, with emphasis on intake of fat, fiber, fruit and vegetables representative for the usual diet.

Methods: A 15–item questionnaire was completed twice in 111 participants in order to study reproducibility. To check its validity, it was compared with a 7–day weighed diet record for 101 subjects.

Results: The participants reported a positive attitude to the questionnaire. Comparing the sum score of the questionnaire and the food record, the reproducibility and validity studies gave correlation coefficients of 0.95 and 0.73 respectively, indicative of good agreement. The reproducibility study showed weighted Kappa coefficients varying between 0.97 for milk and snacks, and 0.75 for vegetables. In the validity assessment, the weighted Kappa coefficients ranged from 0.73 for butter and margarine, to 0.14–0.25 for vegetables, fish and snacks. The correlation coefficient between the sum score of the questionnaire and the percentage of saturated fat in the diet was –0.59.

Conclusions: This simple self-administered questionnaire allows for rapid assessment of constituents of the usual diet in an individual. It gives a good estimation of dietary fat and fiber but is less accurate as regards the intake of vegetables, fish and snacks. It provides an opportunity to discuss central points in the improvement of dietary habits and may be a useful health educational tool in clinical practice.

P1708 Alcohol consumption and clinical, biochemical markers related to cardiovascular disease; a J-shape association

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Background: Alcohol consumption has believed to have ambiguous effect on the cardiovascular risk, especially compared to other well-established risk factors. The aim of this study is to investigate the association between alcohol intake and other clinical and biochemical parameters in cardiovascular disease free men and women.

Methods: The ATTICA study is a prospective population - based cohort designed to enroll 3073 men and women from the greater area of Athens. A random algorithm was developed and stratified, by sex- age; sampling was performed, during 2001. In this work data from 654 men (18-87 years old) and 826 women (18-89 years old) were analysed. Using multiple regression analysis the association between arterial diastolic blood pressure levels, fibrinogen levels, glucose concentration, total cholesterol levels, High and Low density Lipoprotein cholesterol, Apo A-I, Apo B, Lp(a), uric acid, triglycerides, C-reactive protein, homocysteine and alcohol consumption (in wine/glasses per day), were investigated.

Results: A J-shape association was found between alcohol intake (none, 1-2, 3-4, 5+ wine glasses/day) and DBP (76±9 vs. 74±8 vs. 80±10 vs. 86±11 mmHg, P=0.006), SBP (123±29 vs. 121±38 vs. 126±45 vs. 130±41 mmHg, P=0.003), homocysteine (12.9±1.9 vs. 12.1±1.6 vs. 14.5±3.0 vs. 16.5±3.1 mgr/dl P=0.001), blood glucose (93±19 vs. 90±26 vs. 97±30 vs. 99±31 mgr/dl P=0.021), HDL (49±16 vs. 52±17 vs. 47±11 vs. 46±10 mgr/dl, P=0.061), LDL (164±15 vs. 160±18 vs. 173±20 vs. 173±17 mg/dl, P=0.005), Apo A-I (153±35 vs. 168±28 vs. 155±25 vs. 145±25 mg/dl, P=0.026), Apo B (111±26 vs. 108±21 vs. 121±21 vs. 123±17 mgr/dl, P=0.01), Lp(a) (19±3 vs. 18±4 vs. 20±3 vs. 23±5 mgr/dl P=0.021), total cholesterol (214±27 vs. 206±26 vs. 223±28 vs. 226±29 mg/dl, P=0.024), and uric acid (4.26±0.75 vs. 4.09±0.53 vs. 4.76±1.01 vs. 5±1.2 mgr/dl, P=0.009). The previous associations were confirmed (at 5% probability level) from multivariate analysis after taking into account age, sex, smoking habits, lipidemic medication, dietary patterns and physical activity levels.

Conclusions: The controversial association between alcohol intake and cardiovascular disease may be, partially, attributed to the J-shape association between several biochemical markers related to atherosclerosis and the amount of alcohol consumed.

DRUG THERAPY IN HEART FAILURE

P1709 Anticytokine effect of doxycycline in patients with congestive heart failure

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Previous studies have shown increased circulating concentrations of proinflammatory cytokines (CK), such as tumor necrosis factor-alpha (TNF-á) and interleukin-6 (IL-6), and markers of inflammation in patients (pts) with congestive heart failure (CHF). Tetracyclines have recently been shown to exert anti-inflammatory and immunomodulatory activities, independent of their antibiotic properties.

The aim of our study was to estimate 1) the relationship between circulating concentrations of CK, markers of inflammation and hemodynamic parameters in pts with postinfarction CHF, and 2) influence of standard therapy of CHF (ST) and adding of doxycycline (D) on CK levels.

Methods: The study group consisted of 82 pts (age 65.4 ± 1.2 years, infarct age over one year) with CHF [NYHA functional classes (FC) III: 67/82, IV: 15/82]. Echocardiography and 6 minute walking test (6MWT) were performed and blood samples were taken from pts at admission and after four weeks. Serum levels of TNF-á and IL-6 (ELISA), C reactive protein (CRP), fibrinogen (F), and also erythrocyte sedimentation rate (ESR) and white blood cell count (WBC) were determined. ST consisted ACE inhibitors, diuretics, beta-blockers, nitrates and digitalis. D effects were estimated in 51 pts, treated of 4 weeks with D (100 mg/day), adding to ST.

Results: In admission TNF-á concentrations were moderately correlated with FC (r=0.31, p< 0.005), CRP (r= 0.31, p< 0.005), IL-6 (r= 0.51, p< 0.001), left ventricular ejection fraction (EF) (r= -0.32, p< 0.005), 6MWT distance (r= - 0.32, p< 0.005). Levels of IL-6 were strongly correlated with EF (r= - 0.70, p< 0.001), moderately with 6MWT distance (r= -0.55, p< 0.001) and CRP (r= 0.42, p< 0.001) and weakly with ESR (r= 0.23, p< 0.05) and F (r= 0.22, p< 0.05). ST was resulted to significant increasing of EF (at 21.7%, p< 0.01) and 6MWD (at 51%, p< 0.001) and decreasing of IL-6 (at 36.9%, p< 0.01) and CRP (at 35.7%, p<0.001) from baseline. In pts receiving D in addition to ST besides significant increasing of EF (at 23.6%, p< 0.001) and 6MWT distance (at 56.7%, p< 0.001), decreasing of IL-6 (at 53.6%, p< 0.001) and CRP (at 56.7%, p< 0.001), also were shown significant decreasing of TNF-á (at 32.1%, p< 0.001) and F (at 13.7%, p< 0.01) and trend to decreasing of ESR (at 31%, n.s.).

In conclusion, clinical and hemodynamic improvement after ST in pts with severe CHF cause significant decreasing of IL-6, but not TNF-á. However, adding of D to ST leading to decrease the levels of both tested CK and some markers of inflammation.

P1710 Differential systemic and pulmonary haemodynamic effects of systemic selective endothelin A and dual endothelin A/B antagonism heart failure

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Background: Plasma concentrations of endothelin-1 (ET-1) are elevated in patients with chronic heart failure (CHF) and levels correlate with a poor prognosis (Pousset et al 1997). There is evidence that selective ETB blockade results in deleterious haemodynamic changes in CHF with increases in systemic vascular resistance (SVR) suggesting that the balance at the ETB receptor is in favour of vasodilatation (Cowburn et al 1999). However, recent studies have demonstrated that both selective ETA (Spieker et al 2000) and dual ETA/B blockade (Kiowski et al 1995) cause potentially beneficial haemodynamic effects in patients with CHF. Whether selective ETA blockade will have beneficial haemodynamic effects over dual ETA/B blockade has not been previously examined.

Methods: 9 patients with symptomatic CHF (NYHA II-III) were studied in this cross-over randomised controlled trial. Blood pressure and heart rate were measured non-invasively and cardiac output, pulmonary artery and left and right atrial pressure were measured invasively using a pulmonary artery catheter.

Results: Selective ETA blockade increased cardiac output (CO)(p=0.03) and reduced mean arterial pressure (MAP)(p=0.001), systemic vascular resistance (SVR)(p=0.01), mean pulmonary artery pressure (MPAP)(p=0.01), pulmonary vascular resistance (PVR)(p=0.006) and pulmonary capillary wedge pressure (PCWP) (p=0.02).Concomitant ETB blockade attenuated the effects on CCO(p<0.05), SVR (p=0.04), and PVR (p=0.02) but caused a trend towards a further reduction in MPAP and PCWP. Selective ETA blockade did not increase plasma ET-1 concentration whereas concommitant ETB blockade resulted in an increase in plasma ET-1 after both low dose (39±14%, p=0.02) and high dose antagonism (75±24%, p<0.02) thus confirming the role of the ETB receptor in clearance of ET-1.

Conclusions: Chronic heart failure is a leading cause of morbidity and mortality worldwide. Endothelin receptor blockers are being developed as potential therapies in CHF. We have demonstrated significant differences in the effects of selective versus dual blockade of the ET system, whether these potentially benefitial haemodynamic changes will translate into benefits in terms of morbidity and mortality will require large scale clinical trials.

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P1711 Medical therapy in patients with acute cardiogenic pulmonary oedema – What helps, what is harmful? (which is a friend and a foe?)

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Background: Acute cardiogenic pulmonary oedema (CPO) is related with high rehospitalization rate. Patients after CPO receive medical polytherapy although few data are available regarding the efficacy of individual cardiovascular drugs in such scenario. AIM: The aim of this study was to elucidate the safety and efficacy of different cardiovascular drugs used in treatment of patients with acute cardiogenic pulmonary oedema during hospitalisation and two-year follow up. METHODS: 276 consecutive patients (128 males, 148 females; median age 70 years) admitted to two departments of cardiology with CPO between 1998-2000 were retrospectively identified and followed-up for a period of 498±272 days (range 5-932 days), with 94% completeness of follow-up. Ischemic heart disease, hypertension, valvular heart disease and diabetes mellitus were present in 95%, 69%, 33% and 35% of patients respectively. During hospitalisation 58 patients (21%) died and 218 (79%) were discharged. During next two years 13 patients (6%) were lost for follow up. Of those 205 patients discharged from the hospital, an additional 81 (40%) were dead at two years, giving an overall two-year mortality of 53%. Prognostic significance of cardiovascular drugs received in acute and chronic stage was analysed with respect to mortality. RESULTS: Non-survivors more frequently needed intravenous catecholamines (OR=17,89; CI95%; 17,57-18,20; p<0,001), steroids (OR=13,52; CI95%; 13,23-13,81; p<0,001) and morphine (OR=2,16; CI95%; 1,90-2,38; p<0,015) injections whereas less frequently received: angiotensin converting enzyme inhibitors (OR=0,07; CI95%; -0,23-0,36; p<0,001), nitroglycerin (OR=0,16; CI95%; -0,12-0,45; p<0,001), beta-adrenolytics (OR=0,28; CI95%; 0,07-0,62; p=0,002) and acetylsalicylic acid (OR=0,29; CI95%; 0,01-0,58; p<0,001) during hospitalisation. Long-term mortality was associated with digoxin use in hospital (OR=2,4; CI95%; 2,11-2,68; p=0,013) and during follow up (OR=1,97; CI95%; 1,71-2,22; p=0,034). Furthermore, patients who were treated with beta-adrenolytics after hospitalisation had better long-term prognosis (OR=0,54; CI95%; 0,29-0,79; p=0,049). CONCLUSIONS: Treatment with nitroglycerin, beta-adrenolytics, acetylsalicylic acid and angiotensin converting enzyme inhibitors is related to beneficial in-hospital survival. Patients after CPO treated ambulatory with digoxin are at risk of higher mortality whereas the treatment with beta-adrenolytics after hospitalisation is related to favourable long-term survival.

P1712 Combined neurohormonal therapy rather than monotherapy is effective in heart failure patients

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Background: Since landmark trials have established ACE inhibitors (ACEI) and beta-blockers (BB), combined therapy with these substances is recommended in European and US guidelines for the treatment of heart failure patients. However, several studies have clearly shown that both substances are underutilised (ACEI are prescribed in about 50%, BB in about 25% of heart failure patients)
The current study was performed to determine whether optimisation of heart failure therapy translates into improved outcome in clinical practice.
Methods: All patients with systolic heart failure and ejection fraction < 35% referred to the Innsbruck Heart Failure and Transplantation Program between February 2000 and October 2001 were identified. Data of 121 pts. (age 57,2±11,8; males 80,2%; ischemic CMP 36,4%; ejection fraction 21,6±5,4%; LVEDD 69,9±9,9mm; atrial fibrillation 27,3%; heart rate 78,5±15,3 beats/min; RR 119,1±20,5 mmHg; sodium 139,7±4,1mmol/l; creatinine 1,26±0,4 mg/dl) followed for > 40 days (224±164) were analysed. Patients were divided according to their treatment at last follow-up visit into group I: 86 pts. on combined neurohumoral therapy (ACEI and BB) and group II: 35 pts. on neurohumoral monotherapy (ACEI or BB). Outcome was judged by NYHA class and the combined endpoint of death and hospitalisation for worsening heart failure.
Results: There were no significant differences in baseline characteristics among groups. Improvement in NYHA class was significantly higher in group I (2,42±0,77 to 1,8±0,82 vs. 2,6±0,77 to 2,2±0,88, respectively; p=0,028). Likewise, Kaplan-Meier curves examining time to first event of the combined end point showed a clear divergence between the groups (p<0,05). Differences remained significant (p=0,022) after adjusting for NYHA class at referral, age, gender, etiology of CMP, ejection fraction, and atrial fibrillation in Cox regression analysis.
Conclusion: Combined neurohumoral therapy is more effective in heart failure patients than neurohumoral monotherapy, thus emphasizing the need for application of guidelines into clinical practice.

P1713 International variation in the treatment of chronic heart failure with preserved left ventricular systolic function

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Background and methods: There is little information on how physicians treat patients with chronic heart failure (CHF) but preserved left ventricular (LV) systolic function. The Candesartan in Heart Failure - Assessment of Reduction in Mortality and morbidity (CHARM) programme consists of 3 prospective randomised placebo controlled trials, one of which includes 3023 patients with a LV ejection fraction > 40% (the CHARM Preserved trial). This analysis describes geographical variation in the treatment in this patient group. The 26 participating countries were grouped as follows: 1. Belgium, France, Netherlands, Luxembourg 2. UK, Ireland, Australia, South Africa 3. Czech Republic, Hungary, Poland 4. Germany, Switzerland 5. Italy, Spain, Portugal 6. Norway, Denmark, Sweden, Iceland, Finland 7. Russia 8. USA 9. Canada. Malaysia and Singapore [n=70] are not included in this analysis, because of small numbers.

	Geographical region								
treatment (%)	1	2	3	4	5	6	7	8	9
(number of patients)	325	224	196	331	202	431	132	734	378
ACE inhibitors	11	21	5	27	18	8	13	25	30
digitalis	20	25	24	25	31	28	14	37	29
spironolactone	19	16	12	5	21	11	2	11	10
beta-blocker	48	38	69	76	30	56	63	59	52
CCB	25	31	30	18	37	28	22	38	40
nitrates	24	32	59	30	45	28	78	26	31

Conclusions: There is a striking, 2 to 6-fold, regional variation in the use of particular treatments for CHF with preserved LV systolic function. This variation emphasises the lack of evidence to support therapeutic practice and the need for randomised trials in this area.

P1714 Antithrombotic treatment does not seem beneficial in CHF. Interim results of HELAS (HEart failure Long-term Antithrombotic Study)

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Background: The HELAS study (HEart failure Long term Antithrombotic Study) is a multicenter, randomized, double-blind, placebo controlled trial designed to assess and compare relative benefits and risks of already existing antithrombotic treatment (ATT) for patients (pts) with heart failure (HF).
Methods: 332 pts presenting with signs and symptoms of congestive HF and an EF < 35% were enrolled between January 1998 and August 1999. Pts diagnosed with Ischemic Heart Disease (I) were randomized to receive either aspirin (ASA) 325mg or Warfarin (W) whereas pts diagnosed with Dilated Cardiomyopathy (D) were randomized to receive W or placebo (P). The primary endpoint was the composite of non-fatal stroke, peripheral or pulmonary embolism, myocardial (re)infarction, hospitalization (Hosp), exacerbation of heart failure (EX), or death from any cause in the two year follow up period. Altogether, 80% of pts were receiving an ACE inhibitor.
Results: An analysis of the data from the first 450 patient years showed the following incidence of endpoint events per 100 patient years as summarised in the table below. There were no peripheral or pulmonary emboli. Echocardiographic follow up for 2 years showed: An increase in total EF from 28.2±6 to 30.3±7 p<0.05, accounted primarily by D patients EF 27.2±5 to 30.2±9 p<0.05 at two years regardless of P or W while changes were NS for I, regardless of ASA or W therapy.

Observed events/100 patient years

Event	I/ASA	I/W	D/P	D/W
Stroke	2.1	2.1	1.5	0
MI	0	1.1	0	1.3
Hosp/Ex	3.3	12.5	5	4.5
Death	9.3	12.5	9.3	3.1
Hemorrhage	0	6.2	0	4.5

Conclusions: 1)Overall embolic events are few in heart failure regardless of treatment. 2)Treatment does not seem to affect outcome. 3)Co-administration of ACE inhibitors and ASA or W does not influence anatomic and functional state. 4)EF seems to improve in patients who are carefully monitored in a controlled clinical trial. 5)It seems doubtful whether ATT will prove beneficial at the completion of our study.

P1715 Pentoxifylline improves left-ventricular ejection fraction in ischaemic and hypertensive cardiomyopathy

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Introduction: Tumor necrosis factor (TNF)-alpha is significantly elevated in patients with severe congestive heart failure. Pentoxifylline, a xanthin-derived agent, is known to inhibit the production of TNF-alpha. Recent studies have shown benefical effects of pentoxifylline on left-ventricular performance in patients with idiopathic dilated cardiomyopathy [(Sliwa, K. et al. Lancet. 1998,351,1091-93.), (Skudicky, D. et al. Circulation. 2001,103,1083-88.)]. Therefore, we studied the effects of pentoxifylline on left-ventricular function in ischemic and hypertensive cardiomyopathy.
Methods and Results: 30 patients were randomly assigned to pentoxifylline 600mg TID (n=15) or placebo (n=15) if they had a compensated chronic heart failure with a left-ventricular ejection fraction <40% (50% ischemic, 33.3% hypertensive, 16.7% ischemic and hypertensive cardiomyopathy) and had taken their standard treatment consisting of ACE inhibitors, diuretics and β-blockers for at least 3 months. Baseline demographic and clinical characteristics of each group were similar. Primary end point was left-ventricular ejection fraction (LVEF) assessed by contrast two-dimensional echocardiography. Secondary end points were maximal oxygen uptake (VO2max) assessed by cardiopulmonary exercise testing and Minnesota Heart Failure Index. 24 patients completed the study protocoll and were analysed for primary and secondary outcome. After 6 months of treatment, LVEF was significantly higher in the pentoxifylline group than in the placebo group (P=0.03). VO2max and the Minnesota Heart Failure Index were similar in both groups.

Results at Baseline and at 6 Months

	Placebo (n=13)		P	Pentoxifylline (n=11)		P
	Baseline	6 Months		Baseline	6 Months	
LV EDD (mm)	69 ± 7	64 ± 5	NS	68 ± 8	66 ± 9	NS
LVEF (%)	31 ± 7	31 ± 6	NS	31 ± 8	37 ± 13	0.03
VO2max (mL/kg/min)	15 ± 4	18 ± 6	NS	15 ± 5	19 ± 5	NS
Exercise time (min)	9 ± 3	10 ± 4	NS	9 ± 3	11 ± 4	0.05
Minnesota Heart Failure Index	28 ± 14	32 ± 14	NS	34 ± 16	29 ± 22	NS

Conclusion: In patients with ischemic and/or hypertensive cardiomyopathy, the addition of pentoxifylline to standard treatment improves significantly left-ventricular ejection fraction.

P1716 Impact of additional neurohormonal (NH) antagonism in severe CHF patients already receiving a combination of NH antagonists in COPERNICUS

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Background: The results of the Val-HeFT study suggested that broad based neurohormonal blockade may have deleterious effects in patients with heart failure (CHF), but this hypothesis has not been evaluated in other trials.
Methods: The 2289 patients with severe CHF in the COPERNICUS trial were randomized to placebo (PBO) or carvedilol (CRV), which were added to diuretics and an ACE inhibitor (± digitalis) for up to 29 months. Of these patients, 445 were also on spironolactone at baseline and thus received 3 neurohormonal antagonists if they were randomized to CRV. Compared with those not on spironolactone, patients on spironolactone had more advanced CHF at baseline, as reflected by a lower blood pressure and serum Na (both $P < 0.001$) but were similar in other baseline characteristics.
Results: Shown in the Table are 1-year Kaplan-Meier rates and hazard ratios (CRV:PBO) [Cox model]. CRV reduced the risk of a major clinical event in patients on spironolactone to an extent similar to that seen in patients not on spironolactone.

	Spironolactone			No spironolactone		
	PBO (n=225)	CRV (n=220)	Hazard ratio	PBO (n=908)	CRV (n=936)	Hazard ratio
All-cause mortality	19.1%	11.4%	0.65	18.4%	11.3%	0.65
Death or hospitalization for worsening CHF	39.3%	26.3%	0.63	37.5%	25.4%	0.70
Death or cardiovacular hospitalization	41.6%	29.1%	0.61	41.6%	30.4%	0.75
Death or any hospitalization	47.2%	38.4%	0.76	53.3%	42.1%	0.76

Conclusion: These data indicate that the morbidity and mortality of patients with severe CHF receiving drugs that interfere with more than one neurohormonal target can be reduced substantially with further neurohormonal antagonism (with CRV).

P1717 Nitric oxide inhalation in the treatment of right ventricular infarction

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In the treatment of right ventricular infarction maintenance of right ventricular (RV) preload, reduction of RV afterload, inotropic support and early reperfusion are considered to be the mainstays of therapy. However, in some patients volume loading only further elevates the right-sided filling pressure with no improvement in cardiac output. Inhaled nitric oxide (NO) has been shown to reduce RV afterlod by its selective vasodilating effect on the pulmonary vasculature. NO inhalation might be a useful optional therapy by reducing RV afterload in patients with right ventricular infarction not adequately responding to conventional therapy. We therefore investigated the effects of supplemental NO inhalation in the treatment of right ventricular infarction complicated by a low-cardiac-output-syndrome.
Methods: In 10 patients (mean age 67.8 years, range 51-76 years) with coronary artery disease and low-cardiac-output-syndrome following right ventricular infarction (9 postoperative, 1 preoperative) NO-inhalation therapy was initiated in addition to volume loading and inotropic support.
Results: Prior to NO inhalation CVP, PA mean and CI were 18±4 mmHg, 26±8 mmHg and 2.4±0.5 L/min/m^2 with high inotropic support (epinephrine at a mean dose of 0.48±0.13 μg/kg/min). A significant hemodynamic improvement was observed following NO inhalation, administered at a dose of 20-50 ppm. At 24 hours of continuous NO therapy CVP, PA mean and CI were measured to be 11±2 mmHg, 22±6 mmHg and 3.1±0.4 L/min/m^2, respectively. Epinephrine had been progressively reduced to 0.17±0.08 μg/kg/min. NO therapy was successfully weaned at a mean of 50 hours (range 16-74 hours) without hemodynamic deterioration.
Conclusion: In patients with right ventricular infarction and consecutive low-cardiac-output-syndrome supplemental NO-inhalation therapy reduces RV afterload thereby effectively improving cardiac output and may be a promising adjunct to conventional therapy.

P1718 Sensitivity and specificity of a BNP rapid assay in the diagnosis of impalred left ventricular function

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Objective: The sensitivity and specificity of a brain-type natriuretic peptide (BNP) rapid assay (VIVA Diagnostica) for identification of patients with left ventricular dysfunction was investigated.
Patients/methods: In 76 consecutive patients BNP was measured during cardiac angiography. The left ventricular enddiastolic pressure (LVEDP) and the left ventricular ejection fraction (LVEF) were determined as hemodynamic parameters. The threshold for elevated BNP levels was set at 100 pg/ml.
Results: 53/76 patients showed ischemic heart disease (70%). The mean LVEF was 40.6±11%, 30 patients (39.5%) had a LVEF of < 40%. The mean LVEDP was 17.2±6 mmHg, a LVEDP of >20mmHg was measured in 38% of the study patients. The mean BNP value was 225.4±259 pg/ml (range: 2.3-1300). An elevated BNP value of > 100 pg/ml was found in 43/76 patients (57%).
(PPV: positive predictive value; NPV: negative predictive value)

Characteristics	Sensitivity	Specificity	PPV	NPV
LVEDP>20mmHg	82.8%	59.6%	55.8%	84.8%
LVEF< 40%	90%	65.2%	62.8%	91%

Conclusion: The studied BNP rapid assay shows a very high sensitivity in the detection of patients with left ventricular function. The excellent results regarding the negative predictive values underlines the potential relevance of this test in clinical practice.

P1719 Chromogranin and BNP predict prognosis but not hospitalisation in patients presenting with heart failure for the first time

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The serum concentration of chromogranin (CgA) - a chemically and biologically stable Ca^{2+} binding protein co-secreted with many neurohormones - is raised in patients with heart failure, rising with symptom severity. We compare the relative value of serum CgA and plasma B-type natriuretic peptide (BNP) in predicting the prognosis of patients with a new diagnosis of heart failure. Methods: CgA and BNP were measured in 102 patients (68 male; 90% age range 55-88 years) with a new diagnosis of heart failure identified in a population-based study. Patients were prospectively followed up for hospitalisation and death. Median follow-up was 20 months for hospitalisation and 39 months for death. Results: 37 patients died (31 of cardiovascular causes). 27 patients had one or more unplanned hospitalisations for worsening heart failure. Univariate proportional hazards regression indicated that both CgA and BNP at the time of first presentation were strongly associated with survival (Hazard ratio [95% confidence interval] for a doubling in concentration: CgA 2.08 [1.38-3.28]; BNP 2.71 [1.56-4.71]). Multivariate regression suggested that CgA added prognostic information to that provided by BNP alone (multivariate hazards ratio: CgA 1.62 [0.99-2.66], BNP 2.25 [1.28-3.98). Very similar results were obtained when the analysis was restricted to cardiovascular deaths. Neither measure was associated with the likelihood of experiencing an unplanned hospitalisation for worsening heart failure. Conclusion: Both serum CgA and plasma BNP measured at first presentation are strongly associated with subsequent mortality (but not risk of hospitalisation) in a population-based cohort of patients with a new diagnosis of heart failure. Each provides information about prognosis that is unavailable from the other.

P1720 Differential effects of omapatrilat and hydrochlorothiazide on arterial function in hypertension

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Arterial stiffness and elasticity represent relevant factors in the pathophysiology of cardiovascular diseases and exert a major influence on morbidity and mortality. The vasopeptidase inhibitor omapatrilat (Oma) may have beneficial effects on aortic properties above those expected from a decrease in blood pressure. In a double-blind parallel group study, patients with systolic hypertension (SBP 145-179 mmHg) were randomized to: Oma 40 mg qd or hydrochlorothiazide (HCTZ) 25 mg qd (n = 48/treatment) monotherapy for 3 months. Aorto-femoral pulse wave velocity (PWV; sphygmography), late systolic augmentation (applanation tonometry) and total peripheral resistance (TPR) were used to assess the elastic properties of the aorta, large arteries, and arterioles, respectively. The mean changes (± 95% CI) from baseline in supine SBP and resting aortic properties after 3 months of treatment are presented in the table below.

	SBP (mmHg)	PWV (m/s)	Aortic Augmentation Index (%)	Aortic Augmentation (mmHg)	TPR (dyn s/cm^5)
Oma	-30.9* #	-0.79*	-11.9* #	-6.2* #	-14%* #
95%CI	(-34.5,-27.3)	(-1.14,-0.44)	(-15.0,-8.9)	(-7.3,-5.1)	(-0.81,-0.92)
HCTZ	-14.3*	-0.84*	-3.7*	-2.6*	+2%
95%CI	(-18.1,-10.6)	(-1.20,-0.47)	(-6.8,-0.5)	(-3.8,-1.5)	(-0.96,-1.08)

*significant difference to baseline, # significant difference between groups ($p < 0.0001$)

Oma significantly reduced SBP to a greater extent compared to HCTZ. Both Oma and HCTZ reduced aortic PWV to a similar extent: however, aortic augmentation index, aortic augmentation and TPR were significantly reduced with Oma compared to HCTZ.

The study demonstrates that while both drugs favorably influence aortic stiffness, only Oma improves elastic properties of large vascular arteries and arterioles. These properties may have clinical relevance not limited to the treatment of hypertension.

P1721 Effects of enalapril or the endothelin antagonist enrasentan on left ventricular dimensions in patients with asymptomatic systolic dysfunction

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Background: Excessive release of endothelin has been demonstrated in patients with heart failure. The purpose of the present study was to compare the effects of enrasentan (a mixed endothelin receptor antagonist that has been shown to be active in animal models of cardiovascular disease) with enalapril on left ventricular (LV) dimensions and systolic function in patients with asymptomatic LV systolic dysfunction.

Methods: Seventy-two patients (66 males and 6 females, mean (SE) age = 62 ± 1.0) with asymptomatic LV dysfunction (LV ejection fraction <40% for echocardiography or <45% for cardiac magnetic resonance imaging (MRI)) were randomized to receive either enrasentan (90 mg target dose) or enalapril (20 mg target dose). The patients were examined with cardiac MRI at baseline and after 6 months. MRI measures of LV dimensions included: LV end-diastolic (LVEDVI) and end-systolic (LVESVI) volume indices, LV ejection fraction (LVEF) and LV myocardial mass index (LVMI).

Results: Demographic data was comparable between the two groups with respect to sex, age and race. In the enrasentan group, baseline LVEDVI was (mean ± S.E.M) 65 ± 3.0 ml/m^2, the change at 6 months 3.9 ± 1.8 ml/m^2, and for the enalapril group, baseline LVEDVI was 64 ± 3.5 ml/m^2, the change at 6 months -3.4 ± 1.3 ml/m^2 (p=0.001 between groups). The changes in LVESVI were -0.06 ± 1.1 ml/m^2 and -2.0 ± 0.93 ml/m^2 for enrasentan and enalapril, respectively (NS). In the enrasentan group, baseline LVMI was 97 ± 2.6 ml/m^2 and the change at 6 months 0.67 ± 1.6 ml/m^2. For the enalapril group, baseline LVMI was 95 ± 3.7 ml/m^2 and the change at 6 months -3.8 ± 1.6 ml/m^2 (NS). In the enrasentan group, baseline LVEF was 0.65 ± 0.021 and the change at 6 months 0.018 ± 0.008. For the enalapril group, baseline LVEF was 0.63 ± 0.020 and the change at 6 months 0.015 ± 0.010 (NS).

Conclusion: In patients with asymptomatic systolic dysfunction, we found a significant decrease in LVEDVI after 6 months treatment with enalapril when compared to enrasentan. In the present study, treatment with enrasentan was associated with an unfavorable effect on LV dimensions.

P1722 Addition of angiotensin II receptor blockade to angiotensin-converting enzyme inhibition improves baroreflex function in patients with left ventricular dysfunction

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Background: Incomplete suppression of the rennin-angiotensin system (RAS) during long-term angiotensin-converting enzyme (ACE) inhibitors may contribute to increasing sympathetic activity in patients with left ventricular dysfunction (LVD). Combined angiotensin II receptor blockade (ARB) and ACE inhibition completely suppress the activated RAS. However, whether ARB with valsartan improves baroreflex function in patients with LVD already treated with ACE inhibitors is unknown.

Method: We assessed baroreflex control of sympathetic nerve activity and heart rate (HR) in 10 patients with LVD (ejection fraction 38.8±7.2%) receiving long-term ACE inhibitor therapy before and after valsartan (80mg). Arterial baroreflexes were perturbed by bolus administration of phenylephrine. Cardiopulmonary baroreflexes were perturbed by lower body negative pressure (LBNP; -10mmHg). Muscle sympathetic nerve activity (MSNA) was recorded by microneurography.

Results: Resting MSNA did not change after valsartan despite reductions in arterial blood pressure. (from 31.3±9.6 to 28.8±5.3 burst/min) Arterial baroreflex sensitivity improved significantly from 7.6±4.2 to 11.0±6.8 msec/mmHg after valsartan ($p<0.05$). Both arterial and cardiopulmonary baroreflex control of MSNA was enhanced by valsartan (from -40±11% to -55±17% by phenylephrine method, from 25±11% to 58±32% by LBNP method, $p<0.05$).

Conclusion: ARB improves baroreflex control of heart rate and sympathetic nerve activity in patients with LVD already treated with ACE inhibitors.

P1723 Valsartan shows consistent efficacy across heart failure patient subgroups: results from Val-HeFT

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Background: The efficacy of drugs prescribed for heart failure (HF) may be influenced by demographic and/or clinical characteristics. Thus, subgroup analysis is routinely performed in clinical trials to test the general applicability of results. In the Valsartan Heart Failure Trial (Val-HeFT), which compared the angiotensin receptor blocker valsartan to placebo. Valsartan reduced the primary morbidity/mortality endpoint with concordant reductions in subgroups based on patient characteristics. (Cohn & Tognoni, NEJM 2001).

Aims: Here we analyze the efficacy of valsartan on the secondary endpoints of 1st non-fatal morbid (NFM) event (defined as sudden death with resuscitation, therapy for HF, or HF hospitalization), 1st HF hospitalization, and cardiovascular death within non-predefined subgroups based on age, gender, NYHA class, coronary heart disease (CHD) etiology, left ventricular ejection fraction (LVEF), LV internal diastolic diameter (LVIDd) and history of diabetes.

Methods: 5010 patients with mild to moderate HF were randomized to receive either valsartan (force-titrated to 160 mg bid) or placebo in addition to their standard HF therapy. The effect of treatment on the secondary endpoints was evaluated using Cox regression analysis for risk ratio (RR) and log rank test for P-value.

Results: Statistically significant treatment differences and reduced risks of NFM event were observed with valsartan compared to placebo irrespective of age (>=65 years: RR=0.712, p<0.001; <65 years: RR=0.739, p=0.009), gender (Male: RR=0.717, p<0.001; Female: RR=0.742, p=0.013), NYHA class (I-II: RR=0.701, p=0.001; III-IV: 0.742, p=0.001), CHD etiology (yes: RR=0.788, p=0.007; no: RR=0.643, p<0.001) and LVEF (< 27%: RR=0.742, p=0.001; >= 27%: RR=0.707, p=0.001). The RR did favor valsartan in the subgroups of patients with diabetes (RR=0.870, pp=0.281) or LVIDD <3.57 cm/m^2 (RR=0.872, p=0.234) but these differences were not significant as they were in patients without diabetes (RR=0.661, p<0.001) or LVIDD>=3.57cm/m^2 (RR=0.634, p<0.001). Similar results were found for 1st HF hospitalization. Valsartan did not significantly reduce the risk of cardiovascular death for any of the subgroups examined.

Conclusions: Valsartan treatment shows consistent reductions in the risk of NFM event and 1st HF hospitalization across patient subgroups.

CALCIUM AND SIGNAL TRANSDUCTION

P1724 Afterload-induced diastolic disfunction, SERCA2a and PLB gene expression in the development of heart failure

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Load dependence of diastolic function and gene expression of sarcoplasmic reticulum calcium ATPase (SERCA2a) and phospholamban (PLB) were evaluated in the development of heart failure.

The study was carried in the monocrotaline (MCT) model of pulmonary hypertension. Eighteen Wistar rats (10 weeks) were divided to receive either an ip injection of 60 mg/kg of MCT (MCT group; n=8) or a similar volume of the vehicle (Ctrl group; n=10). Four weeks later the rats were instrumented to record left ventricular (LV) pressure and septal-free wall diameter. Beat-to-beat aortic constrictions increased LV pressure from baseline up to isovolumetric. Effects of afterload on relaxation rate were assessed by the % changes in the time constant Tau, while its effects on diastolic function were evaluated by the position of the end-diastolic pressure-diameter (ED-PD) relation. An additional set of animals (n=16; 10 weeks) was divided to receive either a subcutaneous injection of 60 mg/kg of monocrotaline (MCT group; n=8) or a similar volume of the vehicle (Ctrl group; n=8). After 3 weeks, RV free wall samples were collected for SERCA2a and PLB mRNA quantification by RT-PCR using calsequestrin (CSQ) as the house-keeping gene. Results: mean±SEM, $p<0.05$.

In response to aortic constrictions LV pressure increased, in the Ctrl group, from 95±7 mmHg at baseline to 180±6 and 202±7 mmHg in the afterloaded and isovolumetric beats, while in the MCT group it increased from 102±10 mmHg to 181±6 and 206±7 mmHg (p=ns, Ctrl vs. MCT). Tau decreased 25±6% in the afterloaded beats and remained similar in the isovolumetric beats, in the Ctrl group, whereas, in the MCT group Tau increased 24±7% and 49±6% in the afterloaded and isovolumetric beats, respectively. The position of the ED-PD relation was not affected by afterload in the Ctrl group, but it was upward shifted in the MCT group by 1.5±0.6 and 5.2±0.5 mmHg in the afterloaded and isovolumetric beats, respectively. In the MCT group there was a downregulation of RV SERCA2a and PLB mRNA levels, expressed by decreased SERCA2a/CSQ (0,52±0,03 Ctrl vs. 0,24±0,03 MCT) and PLB/CSQ (0,90±0,11 Ctrl vs. 0,48±0,06 MCT) ratios. SERCA2a/PLB ratio was not affected by MCT treatment.

Afterload induced diastolic dysfunction was observed only in the MCT group. Downregulation of SERCA2a and PLB mRNA suggests that afterload-induced diastolic dysfunction might be related to impaired sarcoplasmic calcium reuptake during relaxation. Afterload-induced diastolic dysfunction and impaired calcium handling were, therefore, observed prior to systolic function disturbances.

P1725 S100A1 gene transfer augments Frank-Starling mechanism, Ca^{2+} and β-adrenergic response in engineered heart tissue (EHT)

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Background: Heart failure, characterized by impaired contractile performance and loss of contractile mass is associated with down-regulation of the Ca^{2+} binding protein S100A1 protein. As cardiac tissue engineering is an emerging field which offers new perspectives for tissue replacement therapy, we assessed the effect of gene-transfer of the recently identified novel inotropic factor S100A1 in engineered heart tissue (EHT) which displays characteristic contractile properties of differentiated myocardium. S100A1-supplemented EHT's allowed us to elucidate the impact of S100A1 on (a) length-dependent force-development (Frank-Starling), (b) extracellular Ca^{2+}-stimulated force-generation (Ca^{2+}-treppe) and (c) β-adrenergic response.

Methods and Results: Lattice EHT's from neonatal rat cardiomyocytes and S100A1-adenovirus (SV) were generated according to standard protocols while an adenovirus devoid of S100A1 cDNA served as control (CV). Isometric force of adenovirally transfected EHT's (SV=8 and CV=13; MOI 10 PFU) was measured 12 days after gene transfer at 2 Hz, 37°C and pH 7.4. Western-Blot analysis confirmed a 5-fold S100A1 protein overexpression in SV transfected EHT's (n=4; $P<0.01$) that caused a significant increase of length-dependent maximal isometric force compared to control (mN/mm²; SV 0.37±0.04 vs. CV 0.23±0.03; $P<0.03$). In addition, S100A1 overexpression enhanced both maximal $[Ca^{2+}]_e$-stimulated force-generation by +57% ($P<0.03$) and $[Ca^{2+}]_e$ sensitivity of EHT's (EC50% $[Ca^{2+}]_e$, mM; SV 0.21±0.03 vs. CV 0.33±0.04; $P<0.03$). Moreover, the S100A1-mediated gain in basal contractility was preserved throughout a series of isoproterenol interventions (10-9-10-6 M).

Conclusion: Our study clearly demonstrates that S100A1 gene-transfer in EHT is feasible and augments EHT contractile performance. S100A1 overexpression improved (a) length-dependent force-development (Frank-Starling mechanism), (b) extracellular Ca^{2+}-stimulated force-generation (Ca^{2+}-treppe) and (c) β-adrenergic response. Thus, as S100A1 has recently been identified as a novel inotropic regulator of cardiac contractility, our study provides further insight into S100A1 effects on cardiac contractility while S100A1-supplemented EHT's may provide an interesting tool for cardiac-tissue replacement therapy.

P1726 The sarcoplasmic reticulum Ca^{2+}-load is increased in human failing myocardium by protein kinase A-dependent stimulation

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In human heart failure the activity of the sarcoplasmic reticulum Ca-ATPase has been shown to be reduced, which may be, at least partly, due to a reduced phosphorylation of phospholamban. The present study investigated the functional consequences of reduced SERCA 2a activity in human myocardium. As the Na/Ca exchanger may partly compensate for reduced SERCA 2a-activity in DCM, only DCM with reduced SERCA 2a-activity and normal Na/Ca exchanger-activity were used.

Simultaneous measurements of the intracellular Ca-transient (fura-2 ratio method) and force of contraction were performed in isolated ventricular muscle strips from failing human myocardium (dilative cardiomyopathy, DCM, heart transplants, n=6) in comparison to non-failing myocardium (rejected donor hearts, NF, n=9) at increasing stimulation frequencies (0.5 to 3.0 Hz). In DCM, diastolic $[Ca^{2+}]_i$ was increased and systolic $[Ca^{2+}]_i$ was decreased as compared to NF (0.5 Hz, diastolic $[Ca^{2+}]_i$: 134±27 vs. 73±33 nmol/L; systolic $[Ca^{2+}]_i$: 186±29 vs. 289±63 nmol/L). Only in NF, force and systolic $[Ca^{2+}]_i$ frequency-dependently increased ($p<0.05$). To investigate whether the blunted intracellular Ca-homeostasis in DCM was due to a dysregulation of the Ca-uptake and/or Ca-release from the sarcoplasmic reticulum, the coffeine - induced Ca-release was measured in saponine (5 mg/l, 30 min., 4°C) -skinned fiber preparations in the presence and in the absence of protein kinase A (500 U/ml, 1 h, 20°C, pH 7.5) at constant Ca-loading conditions (pCa 7.0, 30s, 20°C,pH 7.0). Under basal conditions, there was no difference in the coffeine-induced Ca-release as measured by the ratio coffeine-induced force over maximal Ca-induced (pCa 4.5) force (NF: 57±3%, DCM: 68±5%). After incubation in PKA, the ratio coffeine (25 mM)-induced force over maximal Ca-induced force was increased in DCM (96±3%).

Conclusions: The impaired Ca/force-frequency relationship in human failing myocardium may, at least partly, be due to an impaired function of SERCA 2a accompanied by a reduced peak systolic as well as enhanced diastolic Ca-level intracelluarly. Phosphorylation of Ser16-Plb in human failing myocardium is able to improve Ca-release from the sarcoplasmic reticulum and may help to restore the blunted force-frequency relationship in human failing myocardium.

P1727 Baseline hypercontractility and disturbed Ca^{2+} homeostasis in monocrotaline-induced right ventricular hypertrophy of the rat

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Background: Treatment of rats with the Crotalaria alkaloid monocrotaline causes obliterative vasculitis of the lung arterioles which results in increased pressure within the lung circulation and right ventricular (RV) hypertrophy. In some of the animals heart failure develops. The consequences of this hypertrophy for RV myocardial contractility have not been studied in detail. Methods: We examined at 37°C isometric twitches of intact RV trabeculae from rats in the compensated phase of hypertrophy, 20 to 24 days after a single s.c. injection of 50mg/kg monocrotaline (MCT). Control animals were treated with saline. mRNA expression levels were determined using quantitative rtPCR. Protein expression was analyzed using SDS-PAGE and Western blot. Results: Baseline contractility at $[Ca^{2+}]_o$ 1.25mM and 2Hz stimulation rate in MCT preparations was enhanced by 174% compared to controls (P=0.006; n=8 each). In control preparations, raising the stimulation rate resulted in a monotonous increase in developed force, while in MCT preparations the force-frequency relationship was negative, such that at a physiological rate of 5Hz no significant difference in developed force was observed. Examination of the post-rest behavior in MCT preparations compared to controls revealed a dramatic reduction in the ability of the sarcoplasmic reticulum (SR) to accumulate Ca^{2+} during rest intervals exceeding a duration of 2s (P=0.01; n=8 controls, n=9 MCT). SR Ca^{2+}-ATPase (SERCA2a) mRNA expression in MCT myocardium was reduced by 53% (P<0.001; n=8 each), while no significant change in the mRNA expression levels of the sarcolemmal Na^+/Ca^{2+} exchanger was observed. Maximum Ca^{2+}-activated tension was significantly enhanced in Triton X-100-permeabilized MCT preparations (P = 0.013). While control RV myocardium expressed only trace amounts of beta-myosin heavy chain (beta-MHC), 18% of total MHC was present in the beta-isoform in MCT myocardium (P < 0.001). Conclusions: Ca^{2+} homeostasis is substantially impaired in MCT myocardium, resembling that found in other experimental hypertrophy models. A likely cause for this behavior is the reduction in SERCA2a expression levels. Enhanced myofilament Ca^{2+} responsiveness is probably the result of beta-MHC expression and represents a potent compensatory mechanism which explains the baseline hypercontractility.

P1728 The mechanism of pyruvate in human failing myocardium

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Introduction: It is still controversial whether positive inotropic effects of pyruvate are Ca^{2+}-dependent or result from intracellular alkalosis with enhanced Ca^{2+}-responsiveness of myofilaments. We investigated the effects of pyruvate on intracellular pH-changes and of sarcoplasmatic reticulum Ca^{2+}-content in failing and non-failing human myocardium.

Methods: Isolated left ventricular trabeculae from non-failing (n=6) and failing human hearts (n=22) were electrically stimulated (basal stimulation rate 1 Hz, 370C, isometric contractions). A subgroup of muscles was loaded with the fluorescent pH-indicator BCECF-AM (15μM for 45 min). Pyruvate (10 mM) was added under steady-state conditions in bicarbonate-containing buffer. pHi, rapid cooling contractures (RCC's as a measure of sarcoplasmatic reticulum Ca^{2+} content) and force-parameters were recorded. pHi-signals after each experiment were calibrated with the "high-K^+-Nigericin"-method. Average values are given as means ± SEM, analysed by the unpaired students t-test. Values of p<0.05 were considered significant.

Results: Pyruvate increased force of contraction by 82±4% (p<0.05) and RCC amplitudes by 51±3% (p<0.05; rF/rRCC=1.6) in non-failing human myocardium. In failing human myocardium, developed force increased by 67±9% (p<0.05) and RCC amplitudes increased by 29±1% (p<0.05; rF/rRCC=2.3). In parallel, intracellular pH increased from 7.33±0.04 to 7.40±0.04 (p<0.05) in failing human myocardium.

Conclusion: 1. In isolated human myocardium pyruvate induces a Ca^{2+}-dependent and pH-dependent positive inotropic effect. 2. In failing human myocardium the inotropic response was only slightly reduced despite a clear reduction in RCC potentiation. Therefore, intracellular alkalinization may represent a major inotropic mechanism of pyruvate in failing human myocardium.

DIASTOLIC FUNCTION IN HEART FAILURE

P1729 Lean body mass rather than diastolic function predicts exercise capacity in normal older individuals

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The most commonly used measure of aerobic capacity is maximum oxygen consumption during exercise, expressed as millilitres of oxygen per kilogram body weight per minute. Factors that limit maximum exercise capacity, (VO2max) in normal subjects remain disputed. Previous studies have suggested that left ventricular diastolic performance contributes significantly, whilst skeletal muscle mass has been shown to be an independent predictor in subjects with heart failure.

Aim The relative contributions of left ventricular diastolic function, anthropometric variables and resting cardiovascular function to VO2max measured in millilitres per minute were evaluated in 63 healthy, sedentary volunteers using a variety of iterative multiple regression techniques.

Methods VO2max was quantified by respiratory gas analysis during treadmill exercise. It was defined as a plateau in oxygen uptake despite increasing workload, attainment of age-predicted maximum heart rate and a respiratory exchange ratio greater than 1.1. Diastolic function was assessed by measuring Doppler transmitral flow, (E and A velocities) and tissue Doppler imaging of the mitral annulus (E' velocity). Lean body mass was measured using total body dual energy X-ray absorptiometry (DEXA).

Results The subjects had no evidence of cardiovascular disease and had a mean age of 67 years, (range 60-79). Mean BMI was 25.4(± 3.4) and 57% were women. Mean VO2max was 1880 ml/min (range 927 to 3063). In the univariate analysis the only diastolic variable to be positively correlated with VO2max was E/A, p = 0.0035. However, in the multiple regression analysis, lean body mass was the most significant independent predictor of VO2max, explaining 54% of the variance, p< 0.0001. Maximum workload (METS) accounted for an additional 11% of the variance, p = 0.0002, BMI for 7% of the variance, p = 0.0004 and pulse 4%, p = 0.0055.

Conclusions These data suggest that lean body mass is a stronger independent predictor of exercise capacity than diastolic function and other anthropomorphic or resting haemodynamic variables. Correcting absolute VO2 for skeletal muscle mass rather than body weight may therefore enhance the value of VO2max in defining functional status.

P1730 Age-related intramyocardial patterns during diastole in healthy subjects. Analysis with color M-mode Doppler tissue imaging

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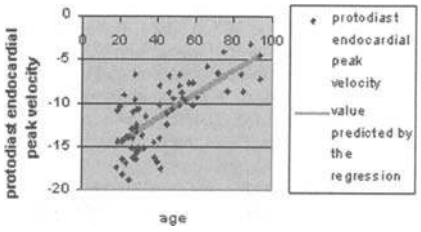
Anatomical changes take place across the left ventricle myocardial wall in the aging heart, with preferential effects in the subendocardium. The aim of this study is to analyse functional correlates of these findings studying the relation of spatial distribution of myocardial velocities (MV) and myocardial velocity gradients (MVG) during diastole with age with color M-mode Doppler Tissue imaging (DTI). Sixty-six healthy subjects, no hypertensive nor diabetic were studied with DTI. Mean age was 42±20 yo. Postprocessing of images was accomplished with propietary software that allows division of myocardial wall in three layers:endo (End), meso (Mes) and epicardium (Epi). MV of all layers and MVG time curves were obtained. Early and late diastolic peak MV were identified.
Results: Peak protodiastolic MV decreased with age in the three layers. Correlation with age was stronger in End (r=0.77, b= 0.135±0.017, p=0.0005) than in Mes and Epi (r=0.62, b=0.088±0.016, p=0.0005 and r=0.5 b=0.053±0.013, p=0.0001), and was comparable to that observed between protodiastolic MVG and age (r=0.82, b=0.122±0.013 p=0.0001). Peak telediastolic MV and telediastolic MVG increased in the three layers (r=0.70 p=0.0005, r=0.68 p=0.0005 and 0.64 p=0.0005 in End, Mes and Epi). Correlation of DTI parameters and mitral flow data was also studied, obtaining an excellent correlation between protodiastolic peak mitral flow and peak protodiastolic endocardial MV (r=0.79, p=0.0005).



Protodiastolic endocardial velocities.

Conclusions: Functional changes in diastolic function related to aging are mainly located in the subendocardium. Protodiastolic endocardial peak MV also showed a high correlation with protodiastolic peak mitral flow confirming that early relaxation depends on the correct performance of subendocardium.

P1731 Body fat mass is a strong predictor of left ventricular diastolic dysfunction: results from a Doppler echocardiographic based survey of a population sample

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An elevated body mass index is associated with a higher prevalence of left ventricular diastolic dysfunction (LVDD). However, it is unclear whether this risk is due to an elevated body fat mass or an elevated fat free mass. Thus, we correlated fat mass with parameters of diastolic dysfunction in a population sample of 1366 men and women aged 25 to 74 years. Left ventricular diastolic function was evaluated echocardiographically (early [E wave] and late [A wave] left ventricular filling as well as isovolumic relaxation). LVDD was defined as proposed by the European Study Group on Diastolic Heart Failure, which allowed adaption of the upper limit for the isovolumic relaxation time and the lower limit for the E/A ratio with increasing age. Fat mass (fat) was determined by bioelectrical impedance analysis and indexed to body weight and body height squared, respectively. In men and in women the E/A ratio decreased and the isovolumic relaxation time (IVRT) increased dramatically with increasing fat/weight and fat/height squared ($p<0.0001$). As a consequence, the crude prevalence of LVDD increased from 6% in individuals in the lowest quartile of fat mass distribution to 16% in individuals beyond the 75% quartile. In both men and women fat mass indices were also correlated with systolic and diastolic blood pressure as well as left ventricular mass. In multivariate analysis, fat mass indexed by weight or height squared could be confirmed as strong independent predictor of an elevated prevalence of LVDD in women (10% increase of risk per 1% higher fat/weight%, OR=1.102 [1.043-1.164], $p<0.0006$). In men, the strong relation between elevated fat mass and LVDD was largely related to concomitant hypertension and LV hypertrophy. In conclusion, body fat mass is a strong independent predictor of diastolic dysfunction in women. In men, fat mass is related with systolic and diastolic blood pressure, as well as left ventricular hypertrophy and, therefore, affects diastolic function "only" indirectly.

P1732 The clinical problem of heart failure with preserved systolic function – a study of incident heart failure presenting in the community

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Background: The clinical syndrome of heart failure (HF) is usually due to a reduction in systolic function (SHF) although HF can occur when systolic function is preserved. If diastolic dysfunction is present the diagnosis of diastolic heart failure (DHF) is then made, although the syndrome of HF can occur with normal systolic and diastolic function.
Methods: One hundred and seventy four consecutive patients with suspected HF referred to a rapid access heart failure clinic (RAHFC) were assessed by history, examination, ECG, CXR, B-type natriuretic peptide (BNP) assay and standard transthoracic echocardiogram (TTE). A panel of 3 cardiologists met to review all cases and determined whether the European Society of Cardiology (ESC) clinical definitions of either systolic or diastolic HF were fulfilled. Those with normal systolic function (ejection fraction >45%) underwent detailed echocardiography measuring diastolic parameters and where appropriate dobutamine stress echo and cardio-pulmonary exercise testing.
Results: Of the 174 patients (median age 72, range 31-90) 36 (21%) were classified by the panel as SHF. A further 49 (28%) had symptoms or signs of HF with objective evidence of a cardiac abnormality. Of these, 21 (12%) had diastolic abnormalities according to ESC criteria. The remaining 28 (16%) had neither systolic nor diastolic abnormalities. There was poor correlation between BNP levels, MVO2 and echocardiographic findings between the three groups.
Conclusions: Over half of all cases considered to have HF according to ESC definitions had preserved systolic function. Only half of these cases had DHF on expert review and only two thirds of them had confirmatory evidence of HF with abnormal BNP or MVO2. An ESC definition of HF with preserved systolic function is required which takes account of clinical, biochemical and physiological criteria.

P1733 The occurrence of left ventricular isolated diastolic dysfunction assessed by Doppler-flow derived parameters in 647 individuals aged 50 to 89

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Background: While comprehensive evidence exists about the prevalence of left ventricular (LV) systolic dysfunction, very scarce data have been published about the occurrence of heart failure on the basis of isolated diastolic dysfunction.
Objectives: To assess the occurrence of LV diastolic dysfunction measured by Doppler-flow derived parameters in an elderly population aged 50 to 89 years in which LV systolic function is preserved.
Methods: A total of 647 subjects (382 female and 265 male, median age 66 years) participated in this cross sectional survey. The study population was recruited from general practitioners and was stratified to include a minimum of 150 persons in each age decade stratum (in the age group 80-89 years, N=100). Each participant answered a heart failure questionnaire, and a clinical examination and an echocardiography were performed. Exclusion criteria were an LV ejection fraction <50% or atrial fibrillation.
Results: Using age- and gender-specific cut-off values for normality of E/A-ratio and deceleration time (DT) as recently published in The Tromso Study, the occurrence of impaired relaxation was 2.7% (95% CI: 1.5-4.1%). However, when fixed cut-off values for subjects above the age of 50 as recommended in the guidelines of 'The European Study Group on Diastolic Heart Failure' were utilized, the corresponding prevalence was 0.5% (95% CI: 0-1.0%). Furthermore, in a subpopulation of 166 participants (mean age 74 + 8 years), the occurrence of pseudonormal filling pattern defined by E/A-ratio between 1.0 and 2.0 and peak E/flow propagation velocity (Vp) >1.5 was 3.6% (95% CI: 0.8-6.4%). About 1/3 of subjects with diastolic dysfunction had complaints of dyspnea.
Conclusion: In this age-controlled population study the occurrence of impaired relaxation as assessed by state-of-the-art Doppler-flow derived parameters was lower using fixed cut-off values for normality of E/A-ratio and DT (prevalence 0.5%) than age- and gender-specific cut-off values (prevalence 2.7%). The occurrence of pseudonormal filling pattern was 3.6%. When correlating these findings to the symptoms reported, only 1/3 of subjects with diastolic dysfunction had complaints of dyspnea. These findings suggest that either diastolic dysfunction is often asymptomatic, or that Doppler-flow derived parameters as a diagnostic method for diastolic dysfunction have a low specificity when used as a screening tool in the general population.

P1734 Significance of early and atrial wave propagation velocity for the differentiation of normal and pseudonormal mitral filling pattern

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Purpose: The assessment of diastolic function limited to mitral inflow pattern analysis is often ambiguous. The occurrence of pseudonormalization requires the incorporation of other parameters for correct diagnosis. We aimed to compare propagation velocity of mitral E and A wave (Ep, Ap) between patients with normal and pseudonormal mitral inflow pattern and to determine optimal cut-off values of Ep and Ap for their differentiation.
Methods: We studied 160 patients (60 after myocardial infarction, 50 with proved coronary artery disease and 50 healthy persons) by transthoracic echocardiography with comprehensive assessment of diastolic function. The subgroup of patients with E/A ratio between 1 and 2, were divided into normal and pseudonormal mitral inflow group according to classic, age adjusted normal values of E wave deceleration time. Ep and Ap were measured in color Doppler M-mode from apical 4-chamber view. Different cutoff values of Ep and Ap for predicting severe diastolic dysfunction were tested.
Results: In pseudonormal group Ep and Ap differed from that measured in persons with normal filling: 27±14 vs 46±9 cm/s, $p<0,0001$ and 36±13 cm/s vs 42±10 cm/s, $p<0,05$. For Ep value below or equal 45 cm/s sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the detection of increased filling pressures (pseudonormal pattern) were: 89%, 54%, 41%, 93%, 63%. For Ep value below or equal 40 cm/s: 83%, 76%, 56%, 93%, 78% respectively and for cutoff 35 cm/s these values were: 83%, 88%, 71%, 94%, 87%.
Ap below or equal 40 cm/s yielded respective values of: 72%, 48%, 33%, 83%, 54%. Ap lower than 35 cm/s: 44%, 70%, 35%, 78%, 63%, Ap lower than 30 cm/s: 39%, 86%, 50%, 80%, 74%. For cutoff value 25 cm/s these values were: 28%, 98%, 83%, 79%, 79%.
For Ep lower than 35 cm/s we have 3 false negative and 6 false positive results. In false negative there was not Ap below 40 cm/s and in false positive there was not Ap below 30 cm/s. Respective values were: false negative Ep: 55,45,60, Ap:67,40,37, false positive Ep: 32,23,35,35,30,31, Ap: 55,34,45,32,40,48.
Conclusions: Ep allows accurate differentiation of normal and pseudonormal mitral flow pattern. However cutoff values lower than commonly recomended 45 cm/s offer better accuracy, with threshold of 35 cm/s being the optimal criterion. Ap is a specific new parameter with high positive and negative predictive value at cut-off 25 cm/s.

P1735 The effects of exercise training on diastolic function in older people: a randomised controlled trial

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Advancing age is associated with significant changes in diastolic function in most healthy individuals. These changes are less marked in master athletes but their permanence and significance in older people is unclear. Studies assessing the effect of exercise training on diastolic function have previously been non-randomised or were in animal models. A randomised controlled trial was therefore performed to assess the effects of exercise training on diastolic function in older people.
Following screening to exclude cardiovascular disease, sedentary volunteers aged 60 to 80 years were randomised to either control or exercise groups. Exercise training consisted of 3 supervised exercise sessions per week for 6 months. The control group maintained pre-randomisation activity levels. Diastolic function was evaluated at baseline and 6 months by measuring Doppler transmitral flow (E and A velocities) and tissue Doppler imaging of the mitral annulus (E' velocity). Body composition was assessed using DEXA imaging and VO2max measured with maximal treadmill testing. Group comparison of parameter changes over the 6-month period was performed.
63 subjects were enrolled in the trial, mean age 67 years (range 60-79), 57% were female. Despite a 13% drop out rate in the exercise group, there was a significant increase in VO2max compared to the control group after 6 months (Table). Trends towards a reduction in heart rate, blood pressure, triglycerides and total body fat and an increase in HDL concentration were noted in the exercise group. However, there were no significant differences in any parameter of diastolic function between the groups (table).

Changes in diastolic parameters

	Control	Intervention	2p
Change in vO2max (ml/kg/min)	-0.5 (3.7)	+4.5 (4.7)	0.0001
Change in E/A	-0.03 (0.2)	0.01 (0.2)	0.78
Change in E' (cm/sec)	0.28 (2.0)	0.48 (1.7)	0.71
Change in E/E'	0.28 (2.0)	0.11 (1.7)	0.64

Conclusions Significant improvements in fitness can be achieved in sedentary elderly volunteers after 6 months of exercise training. Despite this, no statistically significant changes in diastolic function were identified. These data suggest that exercise training does not significantly alter diastolic function in elderly subjects.

NEURO-HORMONAL CONTROL MECHANISMS IN HEART FAILURE

P1736 Skeletal muscle reflex in heart failure patients: role of serum hydrogen

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Background: The overactivity of muscle ergoreceptors (intra-muscular afferents sensitive to metabolites produced by muscle work) may be responsible for the abnormal reflex responses to exercise and for the genesis of symptoms of exercise intolerance in chronic heart failure (CHF). By using interventional methods we sought to identify the role of H^+, K^+, lactate and peripheral haemodynamics on ergoreflex overactivation.
Methods: 10 stable CHF patients (67.9±2.5 years, peakVO2 16.3±1.2 ml/kg/min) and 10 age and sex-matched healthy subjects were studied. The ergoreflex contribution to ventilation was assessed by post handgrip regional circulatory occlusion (PH-RCO) and computed as the difference in ventilation between PH-RCO and a control run without PHRCO. This test was performed on 6 separate occasions. On each occasion a different chemical was infused (insulin, sodium nitroprusside, sodium bicarbonate, dopamine, saline) or a 36-hour glucose free diet was undertaken before the test. During all stages of the protocol, the local muscular blood effluent concentrations of H^+, K^+, glucose and lactate were assessed.
Results: Patients vs. normals had a ventilatory ergoreflex effect on the ventilatory response during the saline infusions (6.7±2.3 L/min v -0.1±0.5 L/min, $p<0.01$). The only intervention to significantly lower the ergoreflex was sodium bicarbonate (0.4±0.3 L/min v -0.2±0.4 L/min on saline, p=NS), which also reduced H^+ concentration during exercise.
Conclusion: A reduction of the serum H^+ concentration by infusion of sodium bicarbonate abolishes the increased ergoreceptor activity in CHF patients. This suggests that H^+ is either a direct mediator or a trigger of such a mediator of the ergoreflex.

P1737 Paradoxical effect of isoprenaline infusion

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Isoprenaline is a beta adrenergic drug used to increase the heart rate and during electrophysiologic study to facilitate the induction of supraventricular and ventricular tachycardias. The purpose of the study was to know the significance of a paradoxical bradycardia induced by isoprenaline infusion.
Methods: electrophysiologic study was performed for the evaluation of tachycardias or dizziness/syncope in 678 patients aged from 15 to 85 years. The study was negative in the basal state; the study was repeated after isoprenaline infusion (20/50 μg).
Results: in most of the patients this perfusion increased the heart rate up to 100/140 beats/min. A bradycardia was noted in 35 patients (5%): 1) Sinus or junctional bradycardia (< 65/min) occurred in 28 pts, aged 15 to 70 years; 25 of them were studied for unexplained syncope; 6 of these patients had a hypertrophic cardiomyopathy; 1 of them developed bradycardia-related atrial fibrillation; other patients had no arrhythmia; 4 young patients (<50 years) were asymptomatic and studied for ventricular or supraventricular tachycardia. 2) Seven other patients developed a second degree AV block which was suprahisian in 3 patients and infrahisian in 4 patients; all patients were studied for exercise-related syncope and AV block was reproduced by ajmaline testing. Isoprenaline has revealed an organic conduction disturbance.
In conclusion the occurrence of paradoxical bradycardia is a rare finding during isoprenaline infusion (5%); it can be without clinical significance in young patients, but was rare (0.5% of the testings). In remaining patients, sinus or junctional bradycardia was associated with hypervagotonia and was more frequent in patients with hypertrophic cardiomyopathy. The development of a second-degree AV block was always pathological and associated with AV conduction disturbances, which occurred spontaneously during exercise.Isoprenaline infusion is a simple means to detect organic AV conduction disturbance especially in patients complaining of exercise-related dizziness/syncope.

P1738 Endothelins and myocardial fibrosis

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The role of endothelins (ET) upon myocardial collagen deposition has been widely studied. Despite of its vasoconstrictor effect ET may work as a mediator of myocardial fibrosis. We investigated in vivo the role of ET on myocardial fibrosis independently of its hemodynamic effects. 40 Wistar male rats were divided into 4 groups: 1) control, 2) sham operated, 3) myocardial infarcted (MI) and 4) MI plus SB209670X (SB), 3mg/Kg bid (ip), an ET A/B blocker. MI was created by LCA ligation and the animals were kept for 4 wk. We evaluated the tail BP before, 2 wk and in the end of experiment. We also evaluated left ventricular end diastolic pressure (LVEDP) before, right after MI and in the end of the study. Interstitial collagen deposition (ICVF) of left and right ventricle (LV, RV) and MI size (IS) were quantifieded by an image system analysis using a picrosirius red stained tissue. We used ANOVA for statistical analysis. The MI size was MI:43.1 ±3.1 and MI+SB 43.3 ±3.3 (p=0.9).

Results:

		CONT	SHAM	MI	MI + SB	p
LVEDP (mmHg)	before	6.1	5.0	6.9	8.0	ns
	after	6.8*	5.2*	11.0	15.0	<0.05
	4wk	5.8*	6.0*	11.6	11.7	<0.05
BP (mmHg)	before	122	116	120	114	ns
	after	128*	110	102	106	<0.05
	4wk	123*	119*	102	103	<0.05
ICVF (%LV)		0.3	0.4	3.0*	1.3	<0.05
ICVF (%RV)		0.5	0.8	1.9*	0.9	<0.05

The ET A/B receptor blockade attenuated myocardial collagen accumulation despite of hemodynamic effects or infarction size. It confirms in vivo that ET stimulate directly myocardial fibrosis as a mediator peptide.

P1739 Left ventricular filling pattern and neurohumoral activation in heart failure. Relationship to exercise tolerance

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Back ground: Heart Failure (HF) is characterized by increased cytokines and natriuretic peptides circulating levels. Left Ventricular (LV) restrictive filling pattern has been recognized as a predictor of a lower survival rate and reduced cardiopulmonary exercise capacity (CPE) in these patients.

Objectives: The purpose of the study was to assess the relationship between LV diastolic filling pattern, circulating proinflammatory cytokines and natriuretic peptides levels and exercise tolerance in patients with Idiopathic Dilated cardiomyopathy (IDC).

Methods: We analyzed circulating levels of Tumor necrosis factor-a (TNF-a)and its receptors, sTNFr1 and sTNFr2, Interleukine-1 (IL-1) and -6 (IL-6), and N-terminal -Atrial (ANP) and brain (BNP) natiuretic peptides by immunoassay, in 90 pts, age 56±12y, with angiographically proven IDC, functional NYHA class II-III and LV ejection fraction 31±9%, in a clinically stable condition during the last month. A complete Echocardiographic study and cardiopulmonary exercise test with a Naughton Protocol was performed on all patients and maximal exercise duration and oxygen consumption at peak exercise (PVO2) were calculated.

Results: According to Doppler transmitral early (Em) to late (Am) filling Velocity or Deceleration Em time (DTE) patients were divided into restrictive (E/A>2 or E/A=1-2 and DTE<140msec, 35 patients) or non-restrictive (55 patients) groups. There was no significant difference in LV dimensions or LV ejection fraction between the two groups. The restrictive Group showed lower right ventricular ejection fraction (EF)(34±10 vs 43±11%, p=0.01) and increased circulating levels of IL-6 (6.8 ± 3.6 vs 3.8±2.8 pg/ml, p<0.001), sTNFr2 (4.09 ±1.6 vs 3.1 ±0.89 pg/ml, p=0.04), ANP (4± 0.7 vs 2.8±1.7 pg/ml, p=0.04) and BNP (1.01± 0.24 vs 0.66 ± 0.33 pg/ml, p=0.03).

Exercise duration (471±243 vs 719±376 sec, p=0.01) and maximal oxygen consumption at peak exercise (17.8±4.8 vs 22.2±6.2 ml/kgr/min, p=0.009) were significantly reduced in restrictive compared to non-restrictive group.

A significant correlation between E/A ratio and IL-6 levels (r=0.29, p=0.01), sTNFR2 levels (r=0.45, p=0.004), BNP (r=0.34, p=0.05), and PVO2 (r=-0.30, p=0.02) was found. The IL-6 was independently associated with E/A ratio(r=0.53, p=0.002.

Conclusions: The restrictive LV filling pattern is associated with increased proinflammatory cytokines and natriuretic peptides levels and impaired exercise tolerance in IDC. The increased LV end-diastolic pressures maybe responsible for the increased neurohumoral activation in those patients.

P1740 Novel, systemic neutral endopeptidase and endothelin converting enzyme inhibition in humans using orally active, SLV 306

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Introduction: Simultaneous manipulation of several endogenous neurohumoral systems is a new and promising therapeutic approach. SLV 306, through its active metabolite KC 12615, has dual neutral endopeptidase (NEP) and endothelin converting enzyme (ECE) inhibiting activity in vitro. The aim of this study was to demonstrate these actions in humans.

Methods: 13 healthy males, studied on 4 occasions, were randomised to placebo or one of 3 doses of SLV 306. Each visit involved, taking a single dose of SLV or placebo, supine rest (3 hours) and infusions of 8 and 12 pmol/kg/min of big ET-1 (20 minutes each). Systolic and diastolic blood pressure (SBP, DBP), ANP, big ET and its cleavage product through the action of ECE on big ET-1, endothelin-1 (ET-1), were measured over 4 hours.

Results: Mean peak changes in SBP (mmHg) after the second big ET-1 infusion were:19.4 (placebo),16.5 (dose 1),14.6 (dose 2),12.9 (dose 3) ($P<0.05$). The respective changes in DBP were 16.2, 14.3, 12.0 and 11.4 ($P<0.05$). The mean, placebo corrected, peptide changes following the second big ET-1 infusion for doses 1, 2 and 3 were; ANP: 7, 11, 15 pg/mL ($p<0.01$), big ET-1: 33, 89, 121 fmol/mL ($p<0.01$) and ET-1: 0.95, 0.56, 0.02 fmol/mL. ET-1 levels did not increase as would have been expected from a pure NEP-inhibitor, whereas big ET levels were increased dose dependently in the SLV 306 groups compared to placebo, indicating that the breakdown of big ET was inhibited. SLV 306 was well tolerated.

Conclusions: This is the first demonstration in humans of both systemic ECE and NEP inhibition. SLV 306, the lead orally active agent in this new class of combined metalloprotease inhibitors, may have therapeutic potential in hypertension and heart failure.

P1741 Sympathetic nerve activity restrains vasodilatory response during exercise in advanced heart failure patients

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We tested the hypothesis that the resting and reflex abnormalities in vascular tone in advanced heart failure patients (HF) are mediated by increased sympathetic nerve activity. Sixteen HF (NYHA, CF= III/IV), and 16 normal controls (NC) were studied. Blood flow was measured in the resting non-dominant forearm with venous occlusion plethysmography at rest and during 3 minutes of isometric exercise (30% MVC). Blood pressure was intra-arterially measured. Saline control (0.5mL/min), phentolamine (100mg/min), or bretylium (2.5mg/min) or acetylcholine (0.64m/min) was infused into the brachial artery. At rest, forearm vascular conductance (FVC) was lower in HF patients than in NC [saline = 0.020±0.002 vs. 0.042±0.01 mL $mmHg^{-1}$ min^{-1} $(100mL)^{-1}$, $P<0.02$)]. Phentolamine or phentolamine plus bretylium significantly increased FVC in HF patients [saline vs. phentolamine (0.020±0.002 vs. 0.055±0.01, $P<0.0001$), vs. phentolamine plus bretylium (0.057±0.01, $P<0.0001$)], and NC [saline vs. phentolamine (0.042±0.01 vs. 0.086±0.02, $P<0.0001$) or vs. phentolamine plus bretylium (0.10±0.02 mL $mmHg^{-1}$ min^{-1} $(100mL)^{-1}$, $P<0.001$)]. At rest, forearm vascular conductance (FVC) with acetylcholine was lower in HF patients than in NC [acetylcholine = 0.059±0.003 vs. 0.188±0.025 mL $mmHg^{-1}$ min^{-1} $(100mL)^{-1}$, $P<0.01$)]. During exercise with phentolamine or phentolamine plus bretylium, the increase in FVC was significantly greater than during saline in HF patients [saline vs. phentolamine (0.001±0.001 vs. 0.02±0.009, $P<0.02$) or vs. phentolamine plus bretylium (0.022±0.008 mL $mmHg^{-1}$ min^{-1} $(100mL)^{-1}$, $P<0.01$)], but no change was found with acetylcholine [saline vs. acetylcholine (0.006±0.002 vs. 0.011± 0.004 mL $mmHg^{-1}$ min^{-1} $(100mL)^{-1}$, $P<0.57$)]. Furthermore, during exercise with saline or acetylcholine the increase in FVC was lower in HF patients than in NC [saline = 0.006±0.002 vs. 0.16±0.053, $P<0.02$; acetylcholine= 0.011±0.004 vs. 0.20±0.069mL $mmHg^{-1}$ min^{-1} $(100mL)^{-1}$, $P<0.002$)], but not during exercise with phentolamine or phentolamine plus bretylium [saline= 0.001±0.001 vs. 0.011±0.004, $P<0.02$; phentolamine = 0.02±0.009 vs. 0.032±0.01, $P<0.49$; phentolamine plus bretylium = 0.022±0.009 vs. 0.03±0.01 mL $mmHg^{-1}$ min^{-1} $(100mL)^{-1}$, $P<0.52$)]. Because sympathetic blockade with phentolamine plus bretylium, in contrast to acetylcholine, dramatically increases FVC compared with saline control in HF patients, and rises FVC to similar levels than NC, we conclude that the increase the sympathetic nerve activity explains, at least in part, the blunted vasodilatory response during exercise in HF patients.

P1742 Relative preservation of the renin-aldosterone system in patients with type 2 diabetes and autonomic neuropathy

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Objective: Autonomic neuropathy (AN) is a very serious and often overlooked component of diabetic neuropathy, which is associated with a reduced 10-year survival rate in type 2 diabetic patients (T2D). Although parasympathetic dysfunction usually antedates sympathetic failure in the natural history of AN, the pathophysiologic mechanisms involved in the progression of AN in humans remain largely unknown. We addressed this issue by investigating the neurohormonal responses during sympathetic activation (orthostatism, O) in subjects with different degrees of AN.
Methods: Plasma noradrenaline (NA, pg/ml), adrenaline (A, pg/ml), renin activity (PRA, angiotensin I, ng/ml/h), and aldosterone (ALD, pg/ml) were measured in the supine position (baseline) and after 2 and 20 min O in 4 groups: 10 healthy subjects (CTR, age 50±12 years, mean±SD), 9 T2D without AN (T2D, 58±7 years), 14 T2D with parasympathetic AN (T2D_PS, 56±4 years), and 7 T2D with sympathetic AN and postural hypotension (T2D_PH, 55±7 years).
Results: See table.

	CTR	T2D	T2D_PS	T2D_PH
NA baseline	181+29	177+84	191+73	103+21
NA 2 min O	292+57***	283+87***	303+110***	181+49**
NA 20 min O	430+154**	393+126***	420+176***	177+96
A baseline	32+12	27+11	22+12	18+11
A 2 min O	53+14***	38+11**	28+20	23+12
A 20 min O	64+20**	49+14***	37+20**	33+20**
PRA baseline	0.59+0.16	0.99+1.00	1.11+0.77	1.28+1.13
PRA 20 min O	2.60+0.44***	2.65+2.29**	2.51+2.68*	2.23+1.48**
ALD baseline	90+44	98+74	90+40	118+75
ALD 20 min O	229+56***	163+62**	150+75***	176+76*

Means+SD; *p<0.05, **p<0.01, ***p<0.001 vs. baseline.

Conclusions: The results show a relative preservation of the renin-aldosterone system (RAS) in advanced AN. By contrast, the impairment of adrenaline response seems to antedate the onset of sympathetic failure whereas the impaired noradrenaline secretion represents a marker of T2D_PH. Although RAS blocking agents may prevent the progression of diabetic neuropathy, their use in advanced AN might potentially exacerbate PH as these patients are highly RAS-dependent.

P1743 Neuroendocrine-mediated induction of interleukin-6 in the heart

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Background: In heart failure blood levels of both noradrenalin and several cytokines among them IL-6 have been found to be chronically elevated, increasing with the progression of the underlying disease. The source of these cytokines as well as possible trigger mechanisms stimulating cytokine release are not yet very well defined.
Methods and Results: IL-6 mRNA expression in left ventricular tissue from patients with severe heart failure is increased compared to healthy donors. Furthermore, transgenic mice with cardiac overexpression of beta1-adrenergic receptor and transgenic rats with overexpression of the human renin and angiotensinogen gene also demonstrated a significant increase in IL-6 mRNA (RT-PCR, Northern blot). Therefore, we examined the putative link between neurohormonal dysbalance with enhanced sympathetic tone and activated renin-angiotensin-system (RAAS) and the release of IL-6 in rat neonatal cardiomyocytes under stimulation with different alpha- and beta-adrenergic agonists, angiotensin II or endothelin. The adrenergic agonists noradrenalin, methoxamin or isoproterenol as well as angiotensin II and endothelin-1 significantly enhanced IL-6 mRNA and protein expression and led to a IL-6 secretion by neonatal cardiomyocytes into the medium. The maximal mRNA induction was detectable after 3 hours, slowly declining within 48 hours after first exposure. A rise in intracellular cAMP by incubation with dbc AMP strongly induced IL-6 and phosphodiesterase inhibtion exaggerated isoproterenol- or noradrenalin-mediated IL-6 release from cardiomyocytes.
Conclusion: Enhanced sympathetic tone and activated RAAS promote IL-6 release from cardiomyocytes, indicating a proinflammatory component of catecholamine and RAAS action and a possible contribution of those mediators to the elaboration of IL-6 in heart failure.

IL-6 expression in cardiomyocytes

	control	noradrenaline	isoproterenol	methoxamine	angiotensin II	endothelin
mRNA	1.08±0.02	1.93±0.02 *	2.26±0.29 *	1.84±0.10 *	1.52±0.06 *	1.76±0.09 *
protein	119±31	299±37	325±66	205±54	256±57	301±35

noradrenaline 10 μM, isoproterenol 10 μM, methoxamine 5 μM, angiotensin II 5 μM, endothelin 0.5 μM, 12 h incubation, n=5 per group, * p<0.05 vs. control.

P1744 Prognostic power of neurohormones depends on the mode of death in patients with chronic heart failure

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Background: Due to increasing therapeutic progress, risk estimation of sudden death and pump failure is getting an important issue. We tested the prognostic power of various neurohormones for prediction of sudden death and pump failure, respectively, and combined the best prognostic markers of each mode of death for a simple risk stratification schedule.
Methods: BNP, N-BNP, N-ANP and big endothelin levels, in addition to clinical and hemodynamic variables, were obtained from 452 patients with a LVEF <35%. For prediction of sudden death and pump failure, two multivariate analyses were performed. Cut-off values were selected to define patients with low and high risk of sudden death and pump failure, respectively.
Results: Up to 3 years, the only independent predictor of sudden death was log BNP (P=0.0006), best independent predictor of pump failure was log N-ANP (P=0.0001). Using Kaplan Meier analysis, significantly fewer patients with BNP<130pg/ml and N-ANP<6300fmol/ml (Group A) died sudden (1%) compared to patients with BNP>130 and N-ANP<6300fmol/ml (Group B; 18%; P=0.0001) and patients with BNP>130fmol/ml and N-ANP>6300fmol/ml (Group C; 19%; P=0.0001). Significantly more patients of Group C (34%) died of pump failure compared to Group B (6%; P=0.0001) and Group A (0%; P=0.0001).
Conclusion: Prognostic power of neurohormones depends on the mode of death. The combined determination of BNP and N-ANP identifies 1) patients with minimal risk of death (sudden 1%, pump failure 0%), 2) patients with elevated sudden death (18%) but low pump failure (6%) and 3) patients with elevated sudden death (19%) and pump failure (34%) risk.

P1745 Fusion pattern of the transmitral flow in patients with heart failure and sinus rhythm

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A restrictive pattern of the transmitral flow has been shown to be associated with high plasma brain natriuretic peptide (BNP) and poor prognosis in chronic heart failure (CHF). However, little is known about the significance of a fusion between the E and the A waves of the transmitral flow in patients with CHF and sinus rhythm.
We studied 213 patients with chronic heart failure due to LV systolic dysfunction (EF < 45%); all patients were in stable conditions for at least 2 weeks; all had a measurement of plasma BNP (RIA) and an echocardiographic study. A restrictive pattern was defined as E/A ratio > 2 or 1<E/A ratio<2 and a deceleration time of E < 130 ms. A non restrictive pattern was defined as E/A ratio < 1 or 1<E/A ratio< 2 and a deceleration time of E > 130 ms. A fusion pattern was defined as an unique diastolic transmitral wave due to superimposed E and A waves. Patients with atrial fibrillation were excluded. After a median follow-up of 2 years, there were 31 deaths and 2 urgent cardiac transplantation. Patients with a fusion pattern had higher plasma concentrations of BNP and a poorer prognosis than patients with restrictive and non restrictive pattern. Among them, a widened QRS was observed in 18/31 (58%) and in patient with normal QRS duration, the heart rate was > 90 bpm in 7/13.

Plasma BNP and mortality

	Non restrictive (n=98)	Restrictive (n=84)	Fusion (n=31)
Plasma BNP (pg/ml)	120±146	214±199*	338± 262*$
One year Mortality	1%	8.6%*	33%*$

* p < 0.01 versus non restrictive; $ p< 0.01 versus restrictive

Thus, a fusion pattern of the transmitral flow is frequently associated with intraventricular conduction disorders or an increased heart rate, and is a marker of severity in patients with CHF in sinus rhythm.

P1746 Correlation of plasma cardiotrophin-1 and exercise derived prognostic indicators in chronic heart failure

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Cardiotrophin-1 (CT-1) a recently identified member of the interleukin (IL) 6 family of cytokines, elevated in the plasma of patients with chronic heart failure (CHF), has previously been shown to correlate with echocardiographic markers of left ventricular dysfunction. We examined the relationship between CT-1 and indicators of exercise capacity in an unselected group of patients with CHF.
86 patients with CHF (mean age 56 years, 84% male, mean LVEF 36.8±2%) and 10 healthy controls (mean age 52 years, 90% male) underwent cardiopulmonary exercise testing with measurement of peak oxygen consumption (VO2) and peak cardiac power output (CPO), both strong predictors of prognosis. A sample of venous blood was obtained and plasma CT-1 was determined using a novel non-competitive two site immunoluminetric assay.
CT-1 levels were elevated in the CHF group (294.7±67.5 fmol/ml, mean±SEM) compared with the control group (94.9±28.0 fmol/ml, $P<0.008$). In the CHF group, there was significant negative correlation of log CT-1 with peak CPO ($r = -0.493$, $p<0.02$), but not with peak VO2 ($r = 0.052$, p=NS). There was no significant correlation between CT-1 and exercise derived data in the healthy control group.
Plasma levels of CT-1 correlated significantly with peak CPO, a strong prognostic exercise derived parameter in CHF. Whether CT-1 will have a predictive prognostic power in CHF remains to be seen.

P1747 17-β-oestradiol in human myocardium: effects on contractile function and intracellular calcium handling

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The heart is a target organ for 17-β-estradiol which has both genomic and non-genomic effects. We investigated the effect of 17-β-estradiol on contractility and intracellular calcium handling in isolated human myocardium.
Methods: Isolated ventricular muscle strips (n=40) from failing human hearts (n=16). Electrical stimulation, 37°C, 1 Hz. Cumulative concentration-response curves (0.1-100 μmol/l) without and with preincubation of a specific estradiol receptor antagonist (ICI 182.780; 1 μmol/l). Additional experiments with a single concentration (10 μmol/l) of estradiol. Simultaneous registration of force of contraction and calcium transients (Aequorin method) or of sarcoplasmic reticulum (SR) calcium content (rapid cooling contractures, RCC).
Results: Estradiol exerted concentration- dependent negative inotropic effects (by maximally 64 ± 4% of basal value at 100 μmol/l; $p<0.05$). The IC50 was 8.2 ± 0.9 μmol/l. ICI 182.780 shifted the concentration- response curve to the right (IC50 for estradiol in the presence of ICI 182.780 was 12.4 ± 1.1 μmol/l, $p<0.05$ vs. estradiol alone). The negative inotropic effects of estradiol (by 36 ± 8% at 10 μmol/l) were associated with a proportional decrease in aequorin light signal (by 38 ± 1%) and a decrease in the amplitude of RCCs (by 19 ± 5%; all $p<0,05$).
Conclusions: Estradiol exerts direct negative inotropic effects in failing human myocardium. These effects are related to depressed intracellular Calcium transients and SR calcium content and at least in part mediated by specific estradiol receptors.

CARDIAC AND VASCULAR ALTERATIONS IN HYPERTENSION

P1748 Changes in geometric adaptation of the left ventricle in hypertensive patients: do they have prognostic significance ?

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Objective: to evaluate the prognostic significance of left ventricular hypertrophy (LVH) regression or persistence as related to changes of LV geometric patterns.
Patients and methods: Five-hundred-twenty-two consecutively seen uncomplicated hypertensive patients underwent baseline echocardiogram for LVMI evaluation and 419 (237 M, 182 F, age range 18-71 years) repeated the echocardiographic examination 2 to 18 years, *mean(SD): 6.2(4.4)*, after the initial study. All but 65 patients received antihypertensive medication during the follow up period. According to the presence of LVH (LVMI > 51 g/ $m^{2.7}$ in both genders) at baseline and at the end of follow-up patients were divided in four groups: with normal LV mass at both examinations (n 205), with regression of LVH (n 59), with persistence of LVH (n 117) and with hypertrophy development (n=38).
Results: Months or years after the follow-up visit 56 patients suffered a first cardiovascular morbid event. Relative wall thickness (RWT) was greater in patients who experienced cardiovascular events then in those patients without events, both at baseline and at follow-up (0.45 + 0.09 vs 0.40 + 0.09 and 0.40 + 0.07 vs 0.38 + 0.07, $p< 0.001$ e $p<0.02$ respectively) After adjustment for traditional cardiovascular risk factors, the cumulative incidence of non fatal CV events was significantly higher in the group of patients without regression of LVH. In all patients the number of morbid CV events was significantly greater in those with a concentric geometry both at baseline and at follow-up in respect to those patients with an eccentric geometry ((38% vs 14%, $p = 0.002$). When considering only patients with LVH at baseline, the number of CV events was greater in those with concentric then in those with eccentric geometry (46% vs 14%, $p = 0.002$). Cox survival analysis showed the presence of LVH at the end of follow up as the most important independent predictor of CV events (Relative risk = 4.58 (2.32-9.03), $p<0.001$) in patients with persistence of LVH and 1.34 (0.46-3.9) in patients with regression of LVH.
Conclusions: These findings strongly confirm that the regression of LVH represents a favourable prognostic index independent from other CV risk factors; changes of LV geometric pattern of adaptation may give additional informations.

P1749 Conversion of atrial fibrillation in hypertensive patients: effects on left atrial size and function

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The aim of the study was to evaluate the Left Atrial (LA) contribution to left ventricular (LV) filling after conversion of atrial fibrillation in hypertrophic hearts. We selected 80 patients (pts) with a first diagnosis of hypertension who had a mild LV hypertrophy. Pts were hospitalized because of an episode of atrial fibrillation and were successfully cardioverted. Pts population included 55 men and 25 women with a mean age of 54 ± 9 years. Pts were compared with a control population of 80 pts cardioverted because of Lone atrial fibrillation without cardiac hypertrophy (mean age 56 ± 12 yrs). Atrial function and size were assessed by Doppler echocardiography and the following parameters were measured: transmitral peak A velocity (A) and integral (Ai), atrial filling fraction (AFF), atrial ejection force (AEF), peak E velocity (E),deceleration time (dec t)and Isolumic relaxation time (IVRT), LA max volume (LA max vol) and minimal volume (LA min vol), LV cardiac mass index (LVMI). Doppler data were correlate to LVMI.
Diastolic function was impaired in the study group: peak E vel was 0,49 ± 0.08 m/sec vs control 0,75 ± 0,10 m/sec ($p<0.01$), peak A vel was 0,79 ± 0.1 m/sec vs control 0,55 ± 0,12 m/sec ($p<0.01$), dec t was 282 ± 39 vs control 201 ± 35 ($p<0.01$), IVRT was 109 ± 15 vs control 88 ± 13. All pts had an increased LVMI (278 ± 47 vs control 110 ± 44 g/m^2; $p <0.001$). AEF increased significantly with age in normal subjects ($r=0.87$; $p<0.001$)and was strongly related to peak A velocity. In hypertensive patients the relation of AEF with age was weak ($r=0.43$; $p <0.05$), the values were significantly higher than in normal subjects. A strong relation was reported between LVMI and AEF ($r=0.75$;$p <0.001$)in the study group while a weaker relation was reported beween LVMI and the other atrial function parameters. LA size was reduced in Hypertensive pts after cardioversion. La max vol decrease from 31 ± 8 to 27 ± 5 cm^3 ($p<0.05$), La min vol decrease from 19 ± 6 to 12 ± 7 cm^3 ($p<0.05$). A relationship between LA maximal and minimal volumes and AEF was observed in hypertensive pts ($r=-0.74$, $p<0.01$ and $r=-0.69$, $p<0.05$)
In conclusion these data suggest that the influence of age in hypertensive pts appeared to be overridden by the effect of the disease process. Hypertrophy had a strong influence on atrial function in pts with hypertension and atrial fibrillation.

P1750 The limited value of plasma B-type natriuretic peptide for identification of left ventricular hypertrophy among hypertensive subjects

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Objectives: Hypertensive left ventricular hypertrophy (LVH) is known to be a strong risk factor for future cardiovascular events. A reduction in LVH during antihypertensive treatment reduces an adverse outcome. Several reports have suggested that plasma B-type natriuretic peptide (BNP) is elevated in hypertensive patients especially with LVH. However, no data have been available concerning the utility of plasma BNP for identifying hypertensive LVH in a screening setting for hypertensive subjects.
Methods: We measured plasma BNP concentrations in 1,586 volunteers in a health screening program (mean age; 56 years). All subjects underwent ECG, chest X-ray, and echocardiography. Patients having typical heart diseases (ie; old myocardial infarction, valvular heart disease, cardiomyopathy, atrial fibrillation) were excluded from the study.
Among the sample, 383 subjects were designated as hypertensive as they were on anti-hypertensive drugs and/or showed elevated systemic blood pressure (>=140 in systolic and/or >= 90 mmHg in diastolic). By echocardiography, 50 of these 383 subjects showed significant LVH (LV mass index > 134 g/m^2 in men and > 110 g/m^2 in women).
Results: Age did not differ significantly between LVH group and non-LVH group (60 ± 9 vs. 59 ± 9 years; NS). Plasma BNP level in LVH group was significantly higher than in non-LVH group (25.1 ± 23.7 vs 18.7 ± 18.9 pg/ml; $p < 0.05$). However, the ability of plasma BNP levels to discriminate LVH patients from non-LVH patients was not sufficient as the area under the receiver-operating characteristic curve was 0.60 (95%CI, 0.55 - 0.65) with sensitivity of 48.0% and specificity of 69.7%. Positive and negative predictive values to select LVH from hypertensive subjects were 19.2% and 89.9%, respectively.
Conclusion: Plasma BNP testing in a mass screening setting is of limited use for identification of LVH patients among hypertensive subjects with heterogeneous etiology.

P1751 Midwall fractional shortening identifies extracardiac organ damage in essential hypertension

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The evaluation of subclinal target organ damage (TOD) is an important task for the stratification of absolute cardiovascular risk profile in essential hypertension (EH). To study the relationship between left ventricular (LV) midwall fractional shortening (MFS) and extracardiac organ damage in a group of 344 untreated hypertensive patients.Left ventricular mass index (LVMI) and function (MFS) were assessed by M-B mode echocardiography (LV hypertrophy LVH= LVMI > 51g/m$^{2.7}$; depressed MFS<14%). Albuminuria was measured as albumin to creatinine ratio (ACR) in three non consecutive first morning urine samples (negative urine culture). Persistent Mi (Alb+) was defined as an average ACR between 2.38-19 (males) and 2.96-20 (females). Carotid wall geometry was evaluated by high resolution US scan, and retinal vascular changes by direct ophthalmoscopy (Keith-Wagener classification).
The prevalence of LV hypertrophy and depressed MFS were 46 and 13% respectively; the prevalence of carotid plaque, microalbuminuria, and retinal changes were 25, 13, and 67% respectively. There were no differences as for blood pressure, lipid profile, smoking habits and alcohol intake among groups of patients divided according to MFS quintiles. Patients in the bottom quintile of MFS showed a higher LVMI (56±2.3, 53±1.9, 54±2, 48±1.8 and 48±1.8 g/m$^{2.7}$ respectively; P<0.01) as well as a higher prevalence of LVH (65, 53, 54, 27, and 32%, respectively; P<0.01) especially concentric hypertrophy (65, 45, 36, 15, and 12%, respectively; P<0.001). Moreover hypertensives with subclinical impairment of LV function, i.e. the bottom quintile of MFS, showed early signs of extracardiac damage, namely increased carotid surface area (CSA) (19.3±2.1, 15,3±0.9, 16.9±2.3, 14.7±1.3, and 13.6±0.9 respectively; P<0.01) and ACR (3.1±0.9, 1.5±0.4, 1.6±0.4, 0.9±0.2, and 0.9±0.2, respectively; P=0.01), a higher prevalence of microalbuminuria (28, 16, 15, 3, and 7%, respectively; P<0.05) and retinopathy (84, 67, 58, 67, and 60%, respectively; P=0.02) compared to the other MFS quintiles. Furthermore, MFS was inversely correlated with mean blood pressure (r= -0.15, P<0.05) and signs of early TOD, namely LVMI (r= -0.23, P<0.01), A/C (r=-0.2, P<0.01), and CSA (r=-0.25, P<0.02). Patients with a depressed MFS show a higher prevalence of LVH and early signs of extracardiac vascular damage. MFS may contribute to identify hypertensive patients at higher cardiovascular profile risk for whom are indicated more aggressive preventive and therapeutic measurements.

P1752 Relationship between weight reduction and regression of hypertensive left ventricular hypertrophy

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Aim of the study is assessment of relationships between weight reduction and regression of hypertensive left ventricular hypertrophy. 73 patients with II-III stage hypertension (43 male), average age 55.9 ± 8 and LVH determinated by echocardiography (average left ventricular mass (LVM) index: 164 ± 32 g/m^2; Penn convention) have been treated (by medication and by diet) for a year. Each subject underwent two-dimensional and Doppler echocardiography, 12-lead electrocardiogram examination, exercise stress testing (Bruce - protocol), 24-h ambulatory monitoring blood pressure (ABPM), 24-h Holter monitoring with Lown classification of ventricular arrhythmia's and heart rate variability. Mean body mass index (BMI) was 28.7 ± 3.6 kg/m^2 (23 to 39), and 28 (39%) patients were obese (BMI > 30 kg/m^2) (OH group). After one year systolic BP (SBP) was reduced on average 168 ± 26 to 158.2 ± 21 mmHg, diastolic BP (DBP) from 102 ± 12.7 to 97 ± 11 mmHg. LV mass index was reduced from 163 ± 32 to 150.2 ± 27 g/m^2 (all p<0.001). 22 patents (30.1%) lost weight more than 5%. These patients significantly decreased LV mass 309 ± 79 vs 278.4 ± 61 g; t=3.22 p<0.004), LV mass index (161 ± 35 vs 148 ± 29 kg/m^2; t=2.68; p<0.02), LV diastolic dimension (52.3 ± 4.7 vs 50.5 ± 4.4 mm; t=2.95, p<0.008), Cornell's index (1.55 ± 0.4 vs 1.41 ± 0.4, p<0.02), peak double product (DP) (27.3 ± 5 vs 24.4 ± 5, t=2.8, p<0.02), DP/METTs (2.48 ± 1 vs 1.84 ± 1, t=2,15; p< 0.05), mean 24h systolic BP (SBP) (144.1 ± 17 vs 138.6 ± 16 mmHg, t=2.2 p<0.04), mean 24h diastolic BP (DBP) (89.5 ± 11 vs 85.7 ± 12 mmHg, t=2.2, p<0.04), mean SBP per day (148.2 ± 18 vs 141 ± 16 mmHg, t=2.6, p<0.02), mean DBP per day (92.7 ± 11 vs 88 ± 13 mmHg, t=2.6, p < 0.02) and increase of mean 24h RR intervals per night (938.2 vs 999 ms; t= 3, p<0,007). Patients (51.70%) who didn't achieve significant loss of weight significantly decreased LV mass index (163 ± 30 vs 152 ± 25 kg/m^2; t=2.1; p<0.05), office SBP (170.3 ± 27 vs 158.9 ± 19, t=2.2, p<0.03), grades of ventricular arrhythmias (2.73 vs 1.95, t=2.1, p<0.04), and mean VES/24h (66.6 vs 20, t=2.22, p<0.04). Hypertensive patients with LVH with significant loss of weight after one year, achieved higher grade of LVH regression (on account of decrease of LV diastolic dimension), lower DP at exercise, lower values of BP during 24-hour monitoring and improvement of heart rate variability, than patients without significant loss of weight.

P1753 Quantification of regional myocardial function improved estimation of coronary flow reserve in left ventricular hypertrophy

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The aim of the study was a quantitative assessment of regional systolic and diastolic myocardial velocities (m.v.) changes in the presence of stress induced myocardial ischemia (m.i.) in hypertensive patients (pts) using pulsed wave Doppler myocardial imaging (PW-DMI).
Methods: We studied forty-three hypertensive pts (29 male, 14 female; mean age 56.8 ± 9.8 years) with left ventricular hypertrophy (LVH) and known or suspected coronary artery disease. In all pts dobutamine stress echocardiography (DSE; from 5 up to 40 mcg/kg/min infused in 3 minute stages plus atropine 1mg if needed) was performed. DSE identified ischemia by the occurrence of wall motion abnormalities (WMA) with stress - positive DSE. Apical views were used to assess m.v. on baseline and at the peak stress. The sample volume was placed in each of the 11 adequately visualized segment in which left ventricle was divided. In each segment peak m.v. of systolic (S), early (E) and late (A) diastolic waves and ratio E/A (index of regional diastolic function) were calculated.
Results: Myocardial velocities were measured in 405 (85.6%) out of 473 possible myocardial segments. During DSE, in 28 (65.2%) pts WMA were detected in 97 (37.1%) out of 262 adequately visualized segments, while in 15 (34.8%) pts WMA were not appeared. In segments with DSE provoked WMA, E decreased from 7.9 ± 3.1 to 6.4 ± 3.5 cm/s (P<0.05), A increased from 9.2 ± 2.9 to 9.8 ± 3.3 cm/s (NS), S decreased from 9.6 ± 3.2 to 8.1 ± 3.4 cm/s (P<0.005) and ratio E/A decreased significantly (P<0.001) compared to baseline values. Out of 143 evaluated myocardial segments in 15 pts with negative DSE, in 4 (26.6%) pts 13 (9.1%) segments demonstrated inversion of E/A ratio after DSE (from 1.02 ±0.08 to 0.91 ± 0.09, P<0.005). Evaluation of m.v. in other 298 segments without WMA showed significant increased of E/A ratio (P<0.001) and S (P<0.005) after DSE.
Conclusion: Quantification of regional m.v. changes during conventional DSE showed that m.i. is associated with significant decreased E/A ratio, S and E m.v. Inverted regional E/A ratio as an earlier diastolic marker of m.i. is superior to WMA in the detection of reduced coronary flow reserve in pts with hypertensive LVH.

P1754 Exercise-induced ischaemia is related to impaired coronary vasodilator capacity and increased pulse pressure in hypertensive patients

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Background: increased Pulse Pressure (PP), i.e. the pulsatile component of arterial pressure, augments the hemodynamic load on left ventricle (LV), promotes LV hypertrophy and represents an independent predictor of cardiovascular risk.
Aim of the study was to investigate the possible relationship between PP, coronary flow reserve (CFR), minimum coronary resistance (MCR), and inducible ischemia in middle-aged hypertensive patients without CAD.
Methods: Sixty-four patients with systo-diastolic hypertension (HBP, 40 males,mean age 53±8 yrs, BP 171±16/100±10 mmHg, LVMI 65±24 g/h2.7)and without significant CAD ruled out by means of symptom-limited stepwise exercise test (bycicle, ETT), high-dose dipyridamole echo (all), and coronary angiography (31 patients), were studied. TEE-Doppler was used to measure coronary flow velocity in LAD at baseline and during dipyridamole infusion (0.84 mg/kg/8 min), and to calculate CFR and MCR. LV mass, mean and relative LV wall thickness (RWT, MWT), and normalized stroke volume/PP, an index of total arterial compliance(AC), were assessed by M-mode US.
Results: ETT was positive for myocardial ischemia (ETT+) in 14 patients, negative in 26 (ETT-) and non-diagnostic in 24. From the lowest to the highest tertile of PP, CFR decreased (2.8±0.4, 2.5±0.5, 2.4±0.3) and MCR increased (1.1±0.2, 1.2±0.1, 1.3±0.2 mmHg*s*cm-1) ($p<0.01$ for the lowest vs the highest tertile); both indexes were comparable through tertiles of mean BP. In univariate regression analysis, CFR was related inversely, and MCR directly, to PP, MWT, and RWT, while CFR was related directly and MCR inversely to AC (r value from 0.25 to 0.40; p from 0.05 and 0.01). In the multivariate model, PP and MWT remained independently related to CFR, and AC and MWT to MCR. Patients with ETT+ had, compared with ETT-, higher PP (74±10 vs 65±12 mmHg) and MCR (1.4±0.3 vs 1.2±0.2), and lower CFR (2.3±0.5 vs 2.7±0.4) and AC (79±18 vs 94±21%) ($p <$ at least 0.05). In the logistic regression, ETT+ was independently associated with AC.
Conclusions: in middle-aged hypertensive patients without CAD, PP comes out as a major factor contributing to a reduced coronary vasodilator capacity and exercise-induced myocardial ischemia. Such an association seems to be at least partially mediated through increased LV wall thickness and impaired arterial compliance.

P1755 Baroreflex control of heart rate and myocardial repolarization in hypertensive patients with renal failure

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Background: Hypertensive patients with renal failure have an increased cardiovascular mortality. Previous studies in patients with various cardiovascular diseases have shown that reduced modulation of heart rate in response to blood pressure fluctuations and altered myocardial repolarization are associated with an adverse prognosis. The aim of the present study was to investigate baroreflex sensitivity and the variability of both heart rate and QT interval in hypertensive patients with renal failure.
Methods: Hypertensive patients (n=77) with renal failure (glomerular filtration rate <20 ml/min) and healthy subject (n=13) were studied. ECG and beat-to-beat blood pressure were continuously registered during 30 minutes rest. Spontaneous baroreflex sensitivity and the numbers of baroreflex-mediated sequences were measured using the sequence method. Heart rate variability in the time domain was calculated as the standard deviation of normal RR intervals and temporal QT variability was calculated as the QT variability index (QTVI) using a validated pattern recognition algorithm.
Results: Hypertensive patients with renal failure had reduced number of baroreflex mediated sequences (24±31 vs 69±10 sequences/1000 beats), reduced baroreflex sensitivity (5±3 vs 9±5 ms/mm Hg) and reduced heart rate variability (21±14 ms vs 40±19 ms), whereas QTVI was increased (-0.70±0.50 vs -1.32±0.26) compared to healthy subjects ($p <0.01$ for all).
Conclusion: Hypertensive patients with renal failure have markedly reduced ability to modulate cardiac parasympathetic nerve activity. This, together with altered myocardial repolarization, may predispose to ventricular arrhythmia and sudden death,

P1756 Nocturnal systolic blood pressure fall

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The purpose of the present study was to evaluate the relation of the nocturnal systolic blood pressure (BP) fall to the carotid lesions and left ventricular (L V) mass index. Also we examine the relation of the nocturnal systolic blood pressure fall to age and parameters derived from the 24h arterial blood pressure monitoring. **Patient population-Methods:** A total of 1544 subjects underwent clinic blood pressure (CBP) readings, 24h ambulatory blood pressure monitoring (AB PM) and ultrasound imaging of the carotid arteries and the myocardium. They had not been given any kind of drug that might have affected their BP level for at least 3 weeks before entering the study. Measurements of 24h arterial BP monitoring (systolic, diastolic and average BP, pulse pressure, abnormal values of systolic/diastolic BP and heart rate), intima-media thickness (IMT) of the carotid arteries and L V mass index were determined in all patients. Their systolic/diastolic 24h ambulatory blood pressure varied from 80/50 to 199/132 mmHg. Three hundred twenty five patients from the total 1544 subjects with known coronary artery disease underwent coronary arteriography and the severity of coronary heart disease evaluated with Gensini score. In order to have the nocturnal systolic BP fall as a continue parameter we calculated the difference between mean daytime -nighttime systolic blood pressure. All subjects were classified into groups by their nocturnal systolic blood pressure fall (extreme-dippers, with >=20% nocturnal systolic BP fall; dippers, with >= 10% but <20% fall; nondippers, with ≥0% but <10% fall; and reverse-dippers, with <0% fall). **Results:** Nocturnal systolic blood pressure fall is related to pulse pressure (multivariate analysis, ABPM derivatives as independent variables, P=0.02, negative), age (bivariate analysis, negative, P=0,00), left ventricular mass index (bivariate analysis, negative, P=0.01), MCCA- IMT (bivariate analysis, negative, P=0.01) but not with Gensini score. There was no difference between men and women in nocturnal BP fall. Left ventricular mass index were significantly higher in nondippers (P=0,00) and reverse -dippers (P=0.02). Mean CCA-IMT was significantly higher in reverse-dippers (P=0.03). Gensini score was significantly higher in extreme-dippers (P=0.04) but the number of patients was very low (n=5). **Conclusions:** Nocturnal BP fall is related to pulse pressure, carotid IMT and L V mass index, indicating that this parameter could be a marker of global cardiovascular risk.

P1757 The "non-dipper" hypertension in the elderly: is it a clinical entity or a bias?

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Introduction: Sleep disturbances are common in the elderly, and they influence the nocturnal blood pressure (BP) determining a "non-dipper"(ND) status (a fall <10% in BP at night), but some data show that the blunted reduction in BP during night could be caused by the discomfort of the ambulatory BP monitoring (ABPM). Actigraphy is a non-invasive and objective method used to estimate sleep-wake schedules by measurement of activity. Our aim is to ascertain whether elderly hypertensive patients (EHP), who experience the discomfort of the cuff-inflation during ABPM, report a poorer quality of sleep able to influence the ND status.
Materials and Methods: Forty-six consecutive EHP (mean age 74.5 ± 6.7 years, 30% males) were evaluated to assess comorbidity (by means of the Cumulative Illness Rating Scale, CIRS), and drug history. Actigraphy (Actiwatch, model AW4, placed on the non-dominant wrist) and ABPM were simultaneously performed for 24 hours.The Sleep Questionnaire (SQ) was administered in the morning before the recording night. Patients were divided in two groups according to the night-time decrease in BP:>10%: dippers (DP, N=29); <10%: non dippers (ND, N=17).
Results: Actigraph data (expressed as mean ± SD) are shown in the table. NDP obtained a higher score to the SQ (4.6±2.9 vs. 3.0±1.1, p=0.030), and used more benzodiazepines (33.1% vs. 10.7%, p=0.035). The mean number of drugs and the CIRS score were higher in NDP (3.6±1.7 vs. 2.7 ±1.6, p=0.046 and 11.0±3.4 vs. 7.9±4.2, p=0.014).

	DP (N=29)	NDP (N=17)	p
Sleep efficiency (%)	87.1±9.7	78.9±11.8	0.022
Actual sleep time (%)	90.7±7.2	83.0±9.9	0.009
Actual wake number	0.5±0.6	1.1±0.9	0.022
N° of immobile phases	98.6±42.4	57.4±31.4	0.002

Conclusions: The actigraphic data demonstrate a poorer sleep quality in NDP; nevertheless, the blunted fall of nocturnal BP of ND group seems independent from the discomfort of the cuff-inflation during night, since they report sleep disturbances in the previous month, with a higher need of benzodiazepines. NDP have a greater comorbidity and polypharmacy, meaning that the ND hypertension in the elderly is not a bias, but it is related to worse clinical conditions that should be studied in depth.

P1758 Is nocturnal pulse pressure useful in predicting of renal function in mild to moderate essential hypertensives?

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The aim of this study was to investigate the relations between glomerular filtration rate and blood pressure (BP) profile parameters in mild to moderate essential hypertensives (EH).
Design and Methods: 120 hospitalized, untreated EH pts (97m, 23f, 50±1y) underwent 24-h BP monitoring (SL-90207). Glomerular filtration rate was assessed by creatinine clearance (Ccr), estimated from serum creatinine values (Cockcroft D., 1976). Pts were divided into three tertiles according to the Ccr: gr.I - 68±1; gr.II - 88±1; gr.III - 112±2 ml/min. Differences between groups were tested by Student t-2 test, the relationship between Ccr and BP parameters - by Pirson correlation analysis. $P<0.05$ was considered statistically significant.
Results: No significant differences have been found between groups by mean age (52±1, 50±1 and 49±1 y) and duration of AH (13±2 10±1; 11±1y). Body mass index was significantly higher in gr.II and gr.III in comparison with gr.I (26±1; 28±1; 30±1 kg/m^2, $p<0.002$). There were no significant differences between groups by mean values of 24-h, day- and nighttime systolic and diastolic BP-s (SBP, DBP). Only nighttime values of pulse pressure (PP) was significantly lower in the gr.II (51±2; 48±1; 52±2 mm Hg, $p<0.04$). Were observed significant relationships between Ccr and nighttime SBP (gr.I - r=-0.38; gr.II - r=0.33; gr.III - r=0.36), DBP (gr.I - r=-0.15; gr.II - r=0.20; gr.III - r=0.32) and PP (gr.I - r=-0.43; gr.II - r=0.31; gr.III - r=0.28).The stronger relationship were observed between Ccr and nighttime PP, but only the low-tertile group presented a negative association. Positive correlations in the gr.II and gr.III, probably showed a presence of compensatory hyperfiltration in EH, which can be conditioned by high hydrostatic pressure. The negative association of reduced Ccr with PP, a correlate of the pulsitile hemodnamic load and conduit vessel stiffness well as an important cardiovascular risk factor, may explain why pts with minor impairment of renal function are at higher risk of cardiovascular events.
Conclusion: These results appeared that the nocturnal PP might be useful in predicting of the hypertension-induced organ damage in particular of renal function.

P1759 Dissociation between the clustering of newer risk factors and estrogen-induced improvement in aortic elasticity in hypertensive women

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It has been suggested that newer risk factors as hyperinsulinemia, hyperhomocystenemia and hyperleptinemia accelerate menopause-induced atherosclerotic process. However, their potential effect on estrogen-induced alteration on aortic elastic properties has not been investigated.
Methods: Towards this end, we evaluated aortic compliance non-invasively on the basis of Doppler ultrasound measurements of pulse wave velocity (PWV) from the carotid to femoral artery by the foot-to-foot method in 52 postmenopausal women (age 53 years, 3.1±1 years after menopause) with untreated, newly diagnosed mild essential hypertension at baseline as well as 20 mins after the sublingual administration of 1mg of 17-â estradiol. Venous blood samples were drawn for determination of insulin, homocysteine and leptin plasma levels according to established methods. All women were free of other cardiovascular risk factors and were without any sign of atherosclerotic disease.
Results: In our women BMI was 29±4 Kgr/m^2, office BP 145/93 mmHg, left ventricular mass index (LVMI) 106±26 gr/m^2, plasma levels of total cholesterol 230±21mg/dl, leptin 34±24 ng/ml, homocysteine 9.5±2 ìmol/l and insulin 12±7 mU/L. Estrogen induced a significant decrease in aortic PWV (236±27 vs 216±22 cm/sec, $p<0.005$) while BP and heart rate values did not change significantly. The aortic PWV, at baseline, as well as the estrogen-induced reduction of aortic PWV were not correlated with the baseline plasma concentrations of insulin, homocysteine and leptin.
Conclusion: Estrogen-induced improvement in aortic compliance is independent of the cluster of newer risk factors in postmenopausal women with mild hypertension.

P1760 Effects of different wines on endothelial function of subcutaneous small resistance arteries of normotensive subjects and hypertensive patients

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In animal models, red wines seem to have a protective effect on the vascular endothelium. However, it is not known whether this effect is present also in human small vessels, and if it is specific for certain wines.
Objective: To investigate the vasodilator effect of different wines in subcutaneous small resistance arteries of normotensive subjects (NT) and of patients with essential hypertension (EH).
Methods: 16 EH and 7 NT were included in the study. Subcutaneous small arteries (relaxed diameter 160-280 mm) were dissected and mounted on a micromyograph. A concentration-response curve (CRC) to acetylcholine (ACH) (cumulative concentrations from 10^{-9} to 10^{-5} mol/L) was performed, after precontraction with norepinephrine 5×10^{-6} mol/L. In addition, the vasodilation produced by different wines was tested as CRC (20, 30 and 50 ml) to: a) a red wine produced "en barrique" (EB), b) a red wine produced in large wood barrels (LB), and c) a red wine produced in steel tanks (ST), after precontraction with norepinephrine 5*10-6 mol/L, in the presence or absence of L-NMMA 100 mmol/L).
The vasodilator response to ACH was greater in NT compared to EH (ANOVA $p<0.001$ between curves). A dose-dependent vasodilator effect of red wines (particularly EB) was detected in both NT and HT. The vasodilation observed with EB and LB involved mainly non-endothelial mechanisms, since it was usually not significantly reduced after pre-incubation with L-NMMA (a decrease was observed only with LB in NT).

Table	50 ml	50 ml + L-NMMA
EB in NT	-65.7±26.8 ***	-69.1±27.5 ***
LB in NT	-47,6±11.1 **	-26.8±16.6*°
ST in NT	-54.4±33.6 *	N/A
EB in EH	-71.9±23.2 ***	-70.1±21.8 ***
LB in EH	-63.2±28.8 ***	-55.3±26.2 ***
ST in EH	-55.8±24.7 *	N/A

Reduction in wall tension in KPa in respect to precontraction; *=p<0.05. **=P<0.01, ***=p<0.001 vs. precontraction, °=p<0.05 vs. 50 ml alone.

Conclusions: Our results suggest that, both in NT and in EH, red wines may possess vasodilator properties, possibly depending on the content of flavonoids or tannic acid. These results may, at least in part, explain the organ-protective properties attributed to a moderate red wine intake.

P1761 Glyceryl trinitrate – A complex vascular intervention resolved by wave intensity analysis

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In an artery, instantaneous wave intensity (WI) measures the balance between forward and backward travelling waves. It has the potential to separate cardiac (forward waves) from microvascular (reflected, backward waves) influences on blood flow. Sublingual glyceryl trinitrate (GTN) is a common intervention with complex effects, including vasodilatation and reflex sympathetic activation. We used WI to resolve the simultaneous upstream and downstream effects of GTN on arterial blood flow.
Methods: WI is the product of derivatives of blood pressure (P) and velocity (U) - dP/dt x dU/dt. A specially designed ultrasound system (Aloka SSD-5500) with B-mode (7.5MHz) and M-mode wall tracking was used to measure non-invasively diameter and velocity waveforms in the right carotid artery. Systemic P was measured and diameter waveforms were converted to P for WI analysis on-line. The system also measured beta, a measure of arterial stiffness. 12 normal subjects (mean age 29 years) were studied on two separate occasions under standardised, controlled conditions. After stable baseline recordings, sublingual GTN (Nitromin spray, 400ug) or matching placebo were administered blind. Paired t tests were used to compare GTN- and placebo-induced changes from baseline.
Results: WI showed two positive peaks, indicating forward waves of cardiac origin in early and late systole. A contractility-related forward compression wave caused initial acceleration and a forward expansion wave caused deceleration and aortic valve closure. In mid-systole, negative WI indicated a backward, reflected wave that increased P and decreased U. GTN caused marked changes in systemic haemodynamics and WI. Diastolic P decreased (-21%, $p<0.01$), consistent with microvascular dilatation, and heart rate increased (+14%, $p<0.01$), consistent with reflex sympathetic activation. Negative WI in mid-systole decreased relative to the forward wave (-27%, $p<0.01$), due to decreased reflection, but the forward compression wave (+41%, $p<0.01$) and beta (+36%, $p<0.01$) increased, due to increases in contractility and arterial stiffness.
Conclusion: This study confirms the potential of WI to resolve complex interventions into upstream and downstream influences on blood flow. In the carotid artery, WI shows that GTN reduces cerebral wave reflection but increases forward compression wave travel from the heart. Arterial stiffness is increased. These changes will be mediated by direct microvascular dilatation and indirect sympathetic activation with increased initial force of myocardial contraction.

P1762 Effect of physical training on arterial stiffness in essential hypertension

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The vascular training is a problem in patients with hypertension. Pulse wave velocity (PWV) is a non-invasive measurement of the mechanical properties of arteries. The aim of this study was to determine the effect of physical training (PT) on arterial elasticity.
Material and methods: The study group consisted of 116 patients with essential moderate arterial hypertension (HA). They were randomised into two groups. Group 1 (65 pts) underwent physical training programme (series of 16 interval trainings on ergometers) and group 2 (51 pts)without PT. Groups were comparable according to age, gender and treatment of HA. The parameters of PWV were evaluated using a computer system Complior. For automatic measurement of PWV pressure waveforms were digitized at rate 500 Hz for carotid femoral distance. 12 healthy volunteers constituted a control group. Arterial elasticity wetre calculated before, post and 3 month after PT.
Results: After 3 momths PWV in control group did not change(7,21± 1,23m/s at baseline vs 7,72±1,31m/s in follow up).
Physical training in group 1 caused the significant reduction of PWV (from 12,8±1,3m/s to 8,1±0,7m/s post PT and 8,7±1,2m/s after 3 months p<0,001).In group 2 PWV was slightly decreassed (from 12,3±1,2m/s at baseline to 11,2±1,3m/s after 3 months period NS).
Conclusion: Physical training in hypertensive patients improves systemic arterial compliance.

P1763 Microalbuminuria is closely related with unfavorable alterations in arterial pressure waveform shape in untreated patients with hypertension

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Although a slight increased urinary albumin excretion (UAE) and an impaired arterial mechanics have both been identified as predictors of cardiovascular events in hypertensive subjects, the interaction between arterial pressure wave (APW) contour and microalbuminuria (MA) has not been well defined
Methods: MA was determined in 3 non-consecutive 24-h urine samples as UAE of 20-200mg/24h in a group of 130 untreated hypertensive subjects. APW was recorded by carotid applanation tonometry and waveform shape was expressed by the augmentation index (AI).
Results: The group of patients with MA(n=48) was matched for demographics with those without MA (n=82). Subjects with MA had significantly increased left ventricular mass index (101 vs 85 g/m^2, p<0.0001), office blood pressure (164/100 vs 146/94 mmHg, p<0.005) and AI (0.16 vs 0.04, p<0.03). Hypertensive patients with A type APW had significant increased values of the log 24-hour UAE compared to those with type B and C type APW. The percentage of patients with A type APW was significantly greater in microalbuminuric patients compared to normoalbuminuric (67 vs 33%, p<0.005); in contrast the percentage of patients with B type or C type APW was significantly greater in normoalbuminuric patients compared to the microalbuminuric patients (68 vs 36%, p<0.005). By multiple regression analysis and analysis of variance it was revealed that increased AI was significantly and independently associated with increased values of UAE (p<0.05).
Conclusion: Hypertensive patients with MA, exhibit an earlier systolic augmentation of arterial pressure reflecting more impaired arterial elasticity compared with hypertensive without MA. These findings may account for the worse cardiovascular outcomes associated with the presence of an increased UAE in hypertensive subjects.

DIRECT PERCUTANEOUS CORONARY INTERVENTION IN ACUTE MYOCARDIAL INFARCTION

P1764 Is the time to treatment of myocardial infarction more important with primary PTCA or with thrombolysis?

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Background: The benefit of thrombolysis in patients with acute myocardial infarction (AMI) strongly depends on the time from the onset of symptoms to the initiation of treatment. For AMI patients treated with PTCA this time seems to be important only to a certain time level.
Objectives: to assess the influence of time to treatment of AMI with coronary angioplasty on short term and long term prognosis.
Methods: We followed 339 consecutive AMI patients treated with coronary angioplasty from 1995 to 1999 in a cardiac care unit in Czech Republic. Patients were divided into 5 groups according to time to treatment. There was no significant difference in gender, localization of AMI, multivessel CAD, diabetes mellitus, hypertension, smoking and Killip class between the groups. Older patients were treated later, patients with prior AMI were treated earlier. 44 (12,9%) patients were in cardiogenic shock in time of admission.
Results: Time to treatment < 1,5h was achieved in 35; 1,5-3,5h in 105; 3,5-5,5h in 72; 5,5-11,5h in 74; 11,5-24h in 53 patients. Ischemic time in the consecutive groups was <2h; 2-4h; 4-6h; 6-12h; I2-24h respectively. TIMI III flow after PTCA was achieved in 93,6% of patients with time to treatment shorter than 3,5 hours and in 83,9% of patients treated later. The lower 30 day mortality (3,6% vs. 11,1%, p=0,012), lower 3 year mortality (8,6% vs. 19,1%, p=0,003), lover frequency of heart failure (11,4% vs. 28,1%, p<0,001) as well as lower maximal level of released kreatinkinase (32+29 vs 44+39 μkat/l, p=0,005) was observed in patients treated within 3,5 hours from symptoms onset compared to patients treated later.
Conclusions: Compared to thrombolysis the succes rate of primary PTCA remains high even if started late. In studied group the patients short term + long term prognosis is best when reperfusion occurred within 4 h. from symptoms onset. After 4th h. the mortality became independent on reperfusion time. Patients without a chance for reperfusion with thrombolytic therapy within 4 h. should be considered candidates for PTCA regardless the time of transportation. In patients with chance to reperfuse infarct related artery within 4h. from symptoms onset with thrombolytic treatment (thrombolysis needs to be started before 2,5 - 3rd h.) while having low probability to start PTCA within 3,5h., the thrombolysis should be given first and PTCA performed later if needed.

P1765 Primary coronary angioplasty versus pre-hospital thrombolysis in acute myocardial infarction: a medico-economic analysis

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Background: The recent CAPTIM study did not demonstrate any significant difference in results between PCA and PHT for the treatment of acute MI concerning the predefined 30-day composite end point (death + recurrent MI + disabling stroke). This analysis aims to assess the in-hospital cost effectiveness of these two widely used reperfusion therapies.
Methods: 217 consecutive patients included in the CAPTIM study in the university hospitals of Grenoble and Lyon were used for this cost analysis (PCA n = 108, PHT n = 109, men = 82%, age = 59 ± 12 yrs). For each individual patient, a real cost analysis was performed based on the costs of pre-hospital care, key hospital resources, duration of hospitalization, medications, biogical and radiological examinations, coronary angiography and angioplasty devices, and staff.
Results: There were no significant differences between the PCA and PHT groups regarding baseline data, clinical presentation, and characteristics of MI. Hospitalization duration was shorter in the PCA than in the PHT group (8.7 ± 6.1 versus 10.3 ± 6.7 days p = 0.08), mainly because of the delay to planned coronary angiography (66 pts - 60%) and elective angioplasty (40 pts - 37%) in the PHT group. Total in hospital real costs were 6675 ± 6504 Euros for the PCA group and 7689 ± 4611 Euros for the PHT group (p = 0.18); 43% of these costs were related to the duration of hospitalization (cf table).
Sixteen patients (7.4%) died during hospitalization, 8 in each group. The additionnal cost per life saved during the acute phase was 1400 Euros in the PHT group when compared to the PCA group, corresponding to a 18% overcost.

Repartition of costs

	PCA	PHT
Pre-hospital care	863 ± 315	1030 ± 361 *
Examinations	1265 ± 1610	1449 ± 1086
Medications	412 ± 988	1008 ± 382 *
Cath. Laboratory	1280 ± 571	916 ± 748 *
Hospital resources	2829 ± 3931	3283 ± 3254

Prices are in Euro. * = p < 0.001 versus PCA

Conclusion: PCA and PHT are equally cost effective for the treatment of acute MI. PCA however allows earlier hospital discharge, and offers appreciable cost saving per life saved when compared to PHT. One year cost effectiveness and cost utility analyses are needed to confirm these results.

P1766 Are mechanical reperfusion results in acute myocardial infarction patients influenced by geographical distribution? Results from the CADILLAC trial

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In the CADILLAC trial, 2082 AMI patients recruited in 76 centers of 9 countries in North America, Europe and South America were randomized to one of four reperfusion strategies: balloon angioplasty (n=517), angioplasty + abciximab (n= 529), Multilink stent (n=512) and stent + abciximab (n=524).The primary endpoint was a composite incidence of death, reinfarction, disable stroke or ischemia driven target vessel revascularization.
In order to determine the possible geographical influence on the clinical outcome, the results of the patients treated in United States (n=1703) were compared with those outside Unites States (n=379).
Results: see table.

US vs non-US patients

	U.S.	Non U.S.	p value
Age	59±12	63±12	<0.001
Prior MI	15%	7.7%	<0.001
Hypertension	35%	27%	0.007
Prior PTCA	12%	5%	<0.001
Prior CABG	2.2%	0.5%	0.002
Symptoms to ER (min)	155±148	194±161	<0.001
ER to procedure (min)	129±117	57±46	<0.001
Anterior location MI	35%	46%	0.001
Pre-procedure TIMI 0/1	67%	76%	0.001
Post-procedure TIMI 3	96%	94%	0.22
MACE at 1-year	17%	15%	0.16
1-year death	3.9%	5.5%	0.19
1-year re-AMI	2.2%	1.6%	0.30
1-year stroke	0.9%	0.8%	1.0
1-year ischemia TVR	13%	8%	0.006

ER = Emergency Room.

Conclusions: In the CADILLAC trial, patients treated in US were younger, but had more prevalence of hypertension and had undergone more often prior revascularization procedures. US patients appeared earlier in the ER, but they had longer delay in receiving reperfusion treatment. The rate of procedural success was similar in both groups. No differences in outcome was observed through one year observation period except less revascularization procedures of the target vessel in the non-US patients.

P1767 In-hospital outcome in octognenarians with acute myocardial infarction undergoing primary coronary angioplasty

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Background: Because elderly patients (pts), especially those 80 years of age or older, have been excluded from most studies of primary coronary angioplasty (PCA) in pts with acute myocardial infarction (AMI), in-hospital outcome in these pts are not well known. The purpose of this study was to evaluate in-hospital outcome in octogenarians with AMI undergoing PCA.
Methods: We analyzed consecutive pts who were 80 years of age or older and underwent PCA within 72 hours onset of AMI between January 1991 and June 2001 at Kokura Memorial Hospital. A multivariable logistic regression analysis was developed to ascertain predictors of in-hospital mortality.
Results: This study population comprised of 237 pts with a mean age of 83.9 ± 3.5 years, 51% of male gender, and 41% with anterior wall localization. Pts underwent PCA within 9.3±12.9 hours from the onset of chest pains and coronary stenting performed in 127 pts (53.6%). The incidence of TIMI 3 flow at the end of PCA was 94.1% and complications associated with PCA occurred in 9.7% (acute closure 7 pts, puncture site bleeding 5 pts, stroke 7 pts, acute renal failure 2 pts, coronary perforation 1 patient and peripheral vascular embolism 1 patient). Overall in-hospital mortality rate was 10.9% and the clinical success (final TIMI 3 flow without death or complications) was achieved in 183 pts (77.2%). Multivariate analysis revealed that cardiogenic shock (OR 5.96, 95%CI 1.26-28.23, p=0.0245), left main disease (OR 7.66, 95%CI 1.09-53.63, p=0.0403), renal dysfunction (OR 13.74, 95%CI 3.32-56.86, p=0.0003), need for IABP (OR 5.16, 95%CI 1.29-20.7, p=0.0205), LVEF<40% (OR 10.92, 95%CI 1.43-83.7, p=0.0241) and coronary stenting (OR 0.096, 95%CI 0.019-0.481, p=0.0043) were significantly associated with in-hospital mortality.
Conclusion: Octogenarinans undergoing PCA could obtain a high rate of final TIMI 3 flow and acceptable clinical success rate, but remained at high risk of complications. Coronary stenting seems to be important to improve in-hospital outcome in octogenarians with AMI.

P1768 Is the outcome different after spontaneous reperfusion (TIMI-3 flow) or direct PTCA for acute myocardial infarction in survivors of out-of-hospital cardiac arrest?

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Background: The outcome of pts presenting with AMI and a spontaneously reperfused (TIMI-3 flow) IRA was demonstrated to be not different when compared to pts with an occluded IRA who underwent successful coronary reopening within 6 hours after the onset of AMI. However, this was not shown in a specific subset of AMI pts in which sudden death has revealed or complicated the acute phase of AMI before the admission in the cath-lab.
Methods and Results: Between Jan 1998 and Dec 2000, 62 survivors of out-of-hospital cardiac arrest (CA) were referred to the catheterization laboratory of our institution. Among them, 45 pts had evidence of acute ischemic syndrome with subsequent coronary artery disease. Direct PTCA was systematically attempted in 25 pts (and successful in 22/25) with significant coronary blood flow reduction (TIMI 0 to 2). Conversely, pts with TIMI-3 flow (N=20) were treated conventionally. There was no difference with regard to mean age, history of prior AMI, diabetes mellitus and total of >60% coronary artery stenosis between the two groups. When compared to pts treated conventionally, pts who were treated by angioplasty had worse LV ejection fraction (31.2%±11.3% vs. 39.3±11.4%, p<0.05) and a higher rate of cardiogenic shock (56% vs. 40%, p<0.05) on admission. Kaplan-Meier survival analysis showed a reduction of 33% in the risk of death from any cause in pts with coronary occlusion who underwent immediate PTCA as compared to those with a patent coronary artery (relative risk, 2.5; Log-rank, p<0.01). By multivariate logistic-regression analysis, PTCA was a strong and independent predictor of survival (0.53; 95% CI, 0.13-0.94; p<0.01).
Conclusion: In pts in which sudden death has complicated the early course of AMI, emergency PTCA appeared as an independent predictor of 6 months survival despite worse baseline characteristics. Randomised studies are required to assess the benefit of direct PTCA in survivors of cardiac arrest with TIMI-3 coronary artery disease.

P1769 Gender differences and angiographic findings in primary angioplasty for acute myocardial infarction

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Background: Female gender may be a risk factor for mortality after acute myocardial infarction, which can not entirely be explained by differences in baseline characteristics. Reports on gender differences in the angiographic findings in patients treated with primary angioplasty have not yet been reported.
Objective: To assess differences in angiographic findings between males and females in a large cohort of patients with primary angioplasty for acute myocardial infarction.
Results: A total of 1702 patients with acute myocardial infarction were studied, consisting of 340 females and 1362 males. Females were older (65 years ± 11.6) than males (59 years ± 11 years, p <0.001). TIMI 3 flow of the infarct related vessel before angioplasty was observed in 14.7% of females compared to 12.8% of males (p=0.35). In females with inferior infarct location, the RCA was the infarct related vessel in 22% compared to 27% in males with inferior location (p=0.2). After angioplasty, there was TIMI 3 flow in 89% of females compared to 91% in males (p=0.3). Myocardial blush grade 2 or 3 after angioplasty was observed in 73% of females compared to 76% in males.
Conclusions: Angiographic findings in primary angioplasty for acute myocardial infarction are comparable between males and females. In both groups there is a high incidence of successful primary angioplasty with TIMI 3 flow and good myocardial blush.

P1770 Primary, rescue, and facilitated PTCA in the community setting: a prospective observation of reperfusion and outcomes in 400 consecutive patients

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Background: Primary PTCA (P-PTCA) is an established treatment in AMI. Rescue PTCA (R-PTCA) may reestablish myocardial perfusion, and possibly save lives. Facilitated PTCA (F-PTCA) may accelerate and improve reperfusion, and save myocardium. The comparative outcomes of these reperfusion treatments in current practice are poorly studied. Purpose: To study the acute outcomes of pts treated with P-PTCA, R-PTCA and F-PTCA in our referral centre, as part of a Quality Assurance protocol. Methods: 400 consecutive pts with high-risk ST elevation AMI (extensive, or recurrent, or with pump failure) <12 h were prospectively included from 1992 through 2001. Pts sent to cathlab for P-PTCA were those admitted to this Hospital, whereas R-PTCA pts were mostly transferred from nearby centres after failed reperfusion and/or with pump failure. F-PTCA (1 r-PA bolus or start of accelerated t-PA, followed by PTCA asap) was begun in Aug. 2000, as a bridge to PTCA when waiting time was >30 min. The angiograms were re-evaluated blindly by 3 operators. Results: P-PTCA, R-PTCA and F-PTCA were actually performed in 282, 82 and 26 pts, respectively. Baseline population data were: age 62±11y, f 16%, diabetics 23%, previous MI 23%, ant.MI 51%, RV MI 24%, leads with ST elevation 5±2, tot ST deviation 19±12mm, time onset-1st Emergency Room (ER) 140±106 min, mv CAD 52%, stent use 70%, gpIIb/IIIa use 16%, and were similar in the 3 cohorts. For P-PTCA, R-PTCA and F-PTCA pts, respectively, time from 1st ER-cathlab was 60±56 min, 161±117 min and 80±51 min (p<.001); Shock on admission was present in 6%, 12% and 0 (p=.052); initial TIMI flow 2-3 was present in 20%, 31% and 58% (p<.001); final flow was TIMI 3 in 75%, 62% and 80% (p=.04); ST resolution was >50% in 65%, 59% and 76% (p=.046); TIMI 3 + >50% ST res. was present in 53%, 42% and 64% (p=.048); Death rate was 9%,12% and 4% (ns); Re-MI was 4%, 4% and 0 (ns); Stroke 1%,1% and 0 (ns); the combined in-hospital end-point of death/re-MI/stroke occurred in 13%, 13% and 0. Conclusions: In our 9-year observation of evolving practice in the community setting, high-risk AMI pts with R-PTCA had a worse risk profile and slightly less favourable acute outcomes than pts with P-PTCA. F-PTCA pts, albeit limited in number and with a better risk profile, had the best vessel patency both before and after PTCA, the most complete ST resolution, and the best acute outcomes. F-PTCA as used in clinical practice deserves more extensive study.

P1771 Transradial coronary intervention for acute myocardial infarction in the elderly ≥ 75 yrs of age: feasibility and in-hospital outcome

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We evaluated the feasibility and in-hospital outcome of transradial coronary intervention (TRI) in elderly patients with acute myocardial infarction (AMI) ≥ 75 yrs of age. From January 1999 to September 2001, 195 elderly patients (81.1 ± 4.6 yrs) with AMI underwent percutaneous coronary intervention (PCI). Among them, TRI could be performed in 165 (84.6%) patients. The remaining 30 patients received PCI from femoral (n = 29) or brachial artery (n = 1) because of cardiogenic shock (n = 22), narrow radial arteries (n = 4) Allen test abnormality (n = 1), chronic hemodialysis patients (n = 1), radial artery spasm (n = 1) and occlusion of subclavian arteries (n = 1). Unless contraindications for radial artery cannulation were present, cardiogenic shock was an independent predictor to limit radial artery approach. Baseline characteristics, procedural and in-hospital outcomes are shown in table.

Baseline characteristics and outcomes

Age (yrs)	81.2 ± 4.7
.Gender (M/F)	91/74
Killip class (I/II/III/IV)	117/34/9/5
Culprit artery (LAD/LCx/RCA/LMT)	69/23/70/3
Lesion type (occluded/A/B1/B2/C)	105/0/9/33/18
Peak CK (IU)	1720 ± 1345
Stent use (%)	83.6
Procedure success (%)	96.4
In-hospital death (Cardiac/Total; %)	6.7/7.9

LAD indicates left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; LMT, left main trank, CK, creatine kinase.

Access site bleeding or hematoma requiring transfusion and procedure related death were not observed in any patients. We conclude that TRI for AMI is feasible and can be performed with high success and low complication rate even in elderly patients ≥ 75 years of age.

P1772 Direct infarct intervention in the diabetic: does it really work?

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Diabetic patients undergoing intervention in coronary heart disease have been shown to be at increased risk for adverse clinical outcomes. Limited data is available on how diabetics fare following direct infart intervention (d-PTCA) in acute MI. We evaluated clinical outcomes following d-PTCA with optimal result in this high-risk clinical subset. From 1/98 to 1/02, 250 patients (male 58%; mean age 63 years) underwent d-PTCA of 271 lesions in 265 vessels. Comorbid risks factors included: age > 70 years, 30.4%; prior MI, 24%; prior CABG, 16.4%; EF < 40%, 33.3%; multi-vessel disease, 21%. Cardiogenic shock was present in 10%. Anterior MI constituted 38.4%. Majority of the lesions (74.9%) were AHA/ACC type B2/C. Stent was deployed in 32%. Patients received ACT-guided IV heparin during the procedure, followed by antiplatelet therapy. Results: Procedural success (TIMI 3 flow; residual stenosis <20%) was obtained in 98%. In-hospital event rate was low: no acute re-closure, 4 (1.6%) CABG, and 1 (0.4%) death. Mean hospital stay was 2.7 days. Mean global LVEF was 42.7% at discharge. There was 1 subacute stent thrombosis. At 12-Month Follow-Up (96.4% complete; mean 6.28 + 4.88 months), the incidence of reinfarction (8.9%), re-PTCA (6%) and stroke (4.4%) were acceptable. Cardiac mortality was 2.2% in the first year following intervention. Event-free survival was seen in 115 patients (86%). Mean LVEF rose to 50.2% at 12-month follow-up (p=0.008).

Conclusions: 1. Direct infarct intervention is safe and effective in diabetic patients presenting with acute MI. 2. Procedural success is high and in-hospital cardiac events are low and comparable to non-diabetics. 3. This translates into low revascularization rates and favorable event-free survival in the long-term. 4) There was highly significant improvement in global left ventricular systolic function at 12-month follow-up. 5) Our data indicates that optimal acute results, both in flow and luminal diameter gain, with prompt and effective salvage of jeopardized myocardium, may be an important determinant in a post-MI diabetic's long-term event free survival.

P1773 Factors influencing the use of primary angioplasty in unselected patients with acute myocardial infarction: results of the AMI-Florence Registry

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Background: Primary angioplasty (P-PTCA) is an effective treatment for patients (pts) with acute myocardial infarction (AMI) presenting with ST segment elevation. As P-PTCA has fewer contraindications than thrombolysis, the availability of P-PTCA should increase the proportion of pts who undergo reperfusion treatment (RT).

Methods: The study was designed as a prospective observational registry including all the Florence area residents who experienced AMI from March 1, 2000 to February 28, 2001. P-PTCA represents the most common modality of RT in the Florence area, which includes 2 high-volume centres with P-PTCA programs and 5 hospitals without the facilities to perform P-PTCA. This analysis refers to the 706 pts with ST-elevation AMI who were admitted within 12 h from symptom onset.

Results: Of these pts, 243 (34.4%) were treated conservatively and 463 (65.6%) received RT: P-PTCA in 423 (59.9%), thrombolysis in 35 (5.0%) and rescue PTCA in 5 (0.7%).The rate of P-PTCA was 85.2% in the 2 centres with P-PTCA facilities and 37.6% (range 17-78%) in the 5 hospitals without (p<0.000). The use of P-PTCA was 66.4% in pts admitted in the office hours and 56.0% in pts admitted in the non-office hours and in the weekends (p=0.004). At multivariate analysis the only factor associated with increased probability of P-PTCA was the admission to a centre with invasive facilities (OR 7.8, 95%CI 5.1-11.8) while factors influencing the exclusion from P-PTCA were age as a continuous variable (OR 0.97, 95%CI 0.96-0.99), history of heart failure (OR 0.26, 95%CI 0.11-0.65), previous myocardial infarction (OR 0.55, 95%CI 0.33-0.93), time from symptom onset to hospital admission as a continuous variable (OR 0.91, 95%CI 0.84-0.99), AMI other than anterior (OR 0.32, 95%CI 0.21-0.50), Killip class 3-4 (OR 0.44, 95%CI 0.24-0.83), admission in non-office hours (OR 0.59, 95%CI 0.39-0.88). In-hospital and 6-month mortality was 5.8% and 8.8% in pts treated with RT vs 14.8% and 23.9% in pts treated conservatively (both p<0.000).

Conclusion: Although P-PTCA can be performed in almost all pts, more than 30% of unselected AMI pts do not actually receive RT. Pts admitted to a hospital with invasive facilities have about eightfold higher probability to be treated with P-PTCA. Pts with a more severe risk profile who are more likely to benefit from the procedure are less likely to undergo it.

P1774 An early revascularization strategy in cardiogenic shock provides similar benefits in men and women

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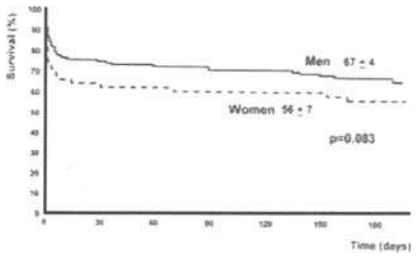
Background: The Shock Trial did not show any benefit of an early revascularization strategy in women with AMI complicated by cardiogenic shock (CS), while the Shock Registry showed similar benefits in men and women.
Methods: Comparison of outcomes of 143 men and 65 women with CS undergoing primary percutaneous intervention (PCI).
Results: Women were older than men (74 ± 10 yrs vs 66 ± 12 yrs, p<0.001). There were no differences between groups in the other baseline characteristics. Primary PCI success rates were similar (95% vs 96%) and coronary stenting was accomplished in most pts of both groups. The six-month survival rate was 56 ± 7% for women and 67 ± 4% for men (p=0.083). There were no differences in reinfarction (2% vs 3%, p=0.619) and target vessel revascularization rates (12% vs 7%, p=0.249). After adjusting for multiple variables, female sex was not related to survival, while the only independent predictor of mortality was age (OR 1.07, 95% CI 1.04-1.09, p<0.001).



Six-month survival.

Conclusion: An early revascularization strategy in patients with cardiogenic shock provides similar effects on outcomes in men and women.

P1775 Primary angioplasty as preferred reperfusion therapy in an unselected population: 6-month follow-up results of the AMI-Florence Registry

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Background: Reperfusion therapy (RT) improves survival in patients (pts) with acute myocardial infarction (AMI). Primary PTCA (P-PTCA) represents the most frequently utilized modality of RT in the Florence area, due to the presence of two high-volume centres with P-PTCA programs.
Methods: The study was designed as a prospective observational registry including all the Florence area residents who experienced AMI from March 1, 2000 to February 28, 2001 and were admitted to hospital within 24 hours from symptom onset. The analysis concerning 806 pts with ST-elevation AMI entered in the registry is presented here.
Results: Mean age was 69.5±13 years, 69% were males, 20.6% had diabetes, 50.4% hypertension, 27% dyslipidemia, 29.3% were current smokers, 15.4% had had a prior myocardial infarction and 6.6% prior revascularization (PTCA or CABG). Killip class >1 was observed in 27.2%; cardiogenic shock was present in 5.2%. Time from symptom onset to admission was <6 h in 82.5%. Among the 494 patients (61.3%) treated with RT, 91.7% underwent P-PTCA. In these pts median door-to-balloon time was 41 min; stents were used in 96%. Overall in-hospital mortality was 9.6%: 6.0% in P-PTCA pts (4.0% in non-shock pts) and 15.7% in pts not treated with RT; one of the 41 pts treated with fibrinolysis died. In P-PTCA pts mortality varied according to time from symptom onset to hospital admission (5.0% if less than 3 hours vs 7.8%, p=0.23) and to door-to-balloon-time (3.0% if time <30 min vs 8.8%, p=0.011).
Overall 6-month mortality was 14.9%: 9.5% in P-PTCA pts, 7.3% in pts treated with fibrinolysis, and 23.7% in pts not treated with RT.
Using a multivariate logistic regression model, Killip >1 (OR 3.9, 95%CI 2.5-6.1), age as a continuous variable (OR 1.08, 95%CI 1.05-1.10), a history of angina (OR 1.61; 95%CI 1.03-2.53) and a previous ictus (OR 2.52, 95%CI 1.30-4.87) were significantly associated with an increase in 6-month mortality, while the use of RT was a protective factor (OR 0.59, 95%CI 0.38-0.93).
Conclusion: P-PTCA, when used as preferred RT, is applicable to a large part of unselected pts with AMI and is associated with excellent 6-month outcome. However, older pts with heart failure at admission and a history of angina or ictus remain at higher risk for 6-month mortality.

P1776 Primary coronary stent implantation for acute myocardial infarction in diabetic versus nondiabetic patients: in-hospital and follow-up results

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Objectives: The outcome of diabetic patients after myocardial infarction (MI) has been worse than in their nondiabetic patients before and during the thrombolytic therapy era. In order to evaluate the impact of diabetes on the acute and late clinical outcomes in a consecutive series of patients undergoing coronary stent implantation in AMI, we compared in-hospital and follow-up clinical outcomes among diabetic and nondiabetic patients.
Material and Methods: From 1997 to 2001 we performed primary coronary stent implantation in 774 patients for acute MI. We compared the angiographic and clinical outcome of nondiabetic (aged 55.9 ± 10.6 years; 82.6% male) and diabetic (aged 56.8 ± 11.7 years; 63.1% male) patients consecutively treated with primary stenting for acute MI. The in-hospital results and follow-up clinical outcomes of each group were retrospectively analyzed.
Results: The nondiabetic group comprised 633 (81.8%) patients and the diabetic group 141 (18.2%) patients. Basic clinical and angiographic characteristics were similar. Angiographic and clinical success was in diabetics = 66.7% and 90.7% vs. in nondiabetics = 78.7% and 95.1% (respectively p=0.006, 0.04). Diabetic patients had a much higher incidence of in-hospital death and overall events (p=0.028). At 1-month follow-up, diabetic patients had a much higher incidence of target vessel revascularization (5.6% vs 1.6%; P = 0.006), which accounted for the majority of the major cardiac events at 1 month (20.6% vs 7.4%; P = 0.003). At a mean follow-up of 7.2 ± 2.7months, 92.9% of nondiabetic and 88% of diabetic patients were alive (p = 0.05). Overall freedom from a major cardiac event (death, MI, target vessel revascularization) at 7.2 ± 2.7month follow-up was 75.8% for nondiabetics and 58.1% for diabetic patients (P <001). By multivariate analysis, age, diabetes, shock, hemodynamic instability and female gender were the most important predictor for development of 1-month and late major cardiovascular events.
Conclusion: Primary stenting in acute MI is effective in restoring immediate TIMI 3 coronary flow in diabetic and nondiabetic patients. This procedure may improve benefit in terms of mortality rate to both groups, particularly in diabetic patients, compared with previous reports with thrombolytic therapy. Nevertheless, major cardiovascular events at 1 month and medium-term follow-up are more frequent in diabetic patients.

P1777 Rescue percutaneous coronary intervention after failed thrombolysis versus primary percutaneous coronary intervention in acute myocardial infarction: registry of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte

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From 1994 to 2000 all PCI-procedures were recorded from 87 German centres. This analysis includes all procedures for AMI <24 h in de-novo coronary lesions:

Rescue vs. primary PCI

	Rescue-PCI	Primary PCI	P=
No.	2210	8736	
% female pts.	22.8	26.5	0.03
age (Y ± SD)	59 ± 12	61 ± 12	<0.001
% 3-vessel-disease	22.6	25.4	0.03
symptoms to PCI (h)	7.1 ± 5.1	5.7 ± 4.9	<0.001
% ST-elevation	94.5	88.8	<0.001
% shock	18.8	14.3	<0.001
% TIMI 0/1 before PCI	66.0	81.5	<0.001
% TIMI 3 after PCI	84.0	86.6	0.03
% stent	60.7	56.2	0.006
max. CK (U/l ± SD)	1249 ± 1275	982 ± 1066	<0.001
% reinfarction	2.6	2.0	n.s.
% in-hospital death	13.4	10.4	0.004

Patients with rescue-PCI were younger, less women, had less 3-vessel-CHD, but longer delay to reperfusion and more shock. Predictors of in-hospital death were shock (OR 17.3; 95%-CI 14.8-20.2), failed PCI (OR 5.1; 4.3-6.1), reinfarction (OR 5.0; 3.5-7.1), age (OR 1.5 per decade; 1.4-1.6), 3-vessel-CHD (OR 1.9; 1.7-2.3), and female gender (OR 1.2; 1.01-1.4). Time to PCI, stent, and maximum CK were not significantly associated with mortality. In multivariate analysis (logistic regression), rescue-PCI had significantly higher mortality than primary PCI (OR 1.25; 95%-CI 1.04-1.50).

P1778 Long-term follow-up after rescue stenting in acute myocardial infarction

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A large amount of clinical data support the concept that stenting in acute myocardial infarction (AMI) represents a feasible and effective revascularization strategy. However, very few information are available in the subgroup of patients (pts) who receive a coronary stent after failed systemic thrombolysis (so-called "rescue" stenting).

Methods: We analyzed long term follow-up (mean 28 months, range 6-85 mo) of 123 consecutive pts (age 60±12 yrs; 78% males) treated with rescue stenting because of persistence or early recurrence of ST segment elevation after full dose TPA (according to GUSTO protocol) in the period 1996-2001.

Results: Coronary stenting was attempted in 123/123 and was successful in 119/123 (96.7%); abciximab was used in 57/123 (46%) and intra-aortic balloon pumping (IABP) in 35/123 (28%). The stented segment was 18±8 mm long. Treated vessel was LAD (48%), RCA (40%), LCX (9%) and vein graft (3%). At the end of the procedure, TIMI 3 flow was obtained in 104/123 (85%) and TIMI 2 in 14 (11%). There were 10 in-hospital deaths and 4 late deaths, with a long term survival of 89%. Target lesion revascularization occurred in 17 cases (14% of discharged pts). Overall, event-free survival was 77%. Predictors of in-hospital mortality were all clinical parameters of high risk: age (p=0.01), Killip class 4 (p<0.001), cardiac arrest (p=0.009), 3 vessel or left main disease (p=0.02), ejection fraction (p<0.001) but not pre-coronary time, infarct location or use of abciximab or IABP. Predictors of late mortality were: age (p=0.007), peak troponin I (p=0.01) and previous infarction (p=0.006). TIMI flow <3 post-procedure has a negative impact on early (p=0.008) but not late mortality. At multivariate analysis, independent predictors of survival were age (p=0.014) and ejection fraction (p=0.006).

Conclusions: These data are among the few available concerning long term follow-up after rescue stenting and show that late mortality is relatively low, comparing favourably with results obtained in primary stenting. Although the scenario of percutaneous revascularization in AMI represents a field of rapidly evolving strategies, these data suggest that rescue stenting should not be denied to appropriately selected patients after failed thrombolysis.

P1779 Effect of abciximab and adenosine on microvascular reperfusion during direct angioplasty for acute myocardial infarction

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Background: Despite early recanalization of an occluded infarct artery, up to one third op the patients still fail to obtain complete myocardial reperfusion and remain at risk of developing large infarcts. This study sought to assess whether adjunctive therapy with abciximab and adenosine might attenuate this process of impaired microvascular reperfusion and its detrimental implications.

Methods and Results: Microvascular reperfusion was studied in 200 patients with AMI by evaluation of the resolution of ST-segment elevation after successful percutaneous coronary intervention (PCI). An historical cohort of 102 patients receiving no adjunctive therapy constituted the control group (G1). A total of 5O patients received adjunctive therapy wiht abciximab alone(G2) and 48 patients received combined adjunctive therapy of IV abciximab and intracoronary infusion of adenosine during PCI (G3).The phenomenon of impaired microvascular reperfusion defined as the presence of persistent (>50% of initial value)ST segment elevation despite successful recanalization (%ST > 50%), occurred in 17% of G3 vs 37% in G2 vs 33% in G1 (p=0.01).Multivariate analysis identified combined adjunctive therapy (G3) as an independent protective factor for microvascular reperfusion. Major cardiac event rate (death and MI) at one month tended to be lower in patients receiving adjunctive treatment: 10% in G1 vs 6% in G2 and vs 7% in G3. This positive effect on clinical outcome was mainly observed in the 61 patients with impaired reperfusion (%ST > 50%) and was related to abciximab treatment: MACE rate of 23% in G1 vs 11% in G2 vs 12% in G3. The outcome of the 139 patients without impaired microvascular reperfusion was excellent for all studygroups (MACE rate: 3%, 5%, 5%)

Conclusion: Adjunctive therapy with abciximab and adenosine during PCI for AMI has a beneficial effect on outcome: it attenuates the process of microvascular reperfusion injury (mainly adenosine effect) and it seems to prevent thrombotic complications particularly in patients with impaired microvascular reperfusion (mainly abciximab effect)

P1780 Abciximab use in unselected patients with acute myocardial infarction treated with primary PTCA: data from the AMI-Florence Registry

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Background: Factors influencing the use of abciximab (ABC) in unselected patients (pts) with acute myocardial infarction (AMI) treated with primary PTCA (P-PTCA) have not been fully explored yet. Furthermore, the potential benefit of ABC treatment in this population remains controversial.

Methods: Data are derived from the AMI – Florence Registry, a prospective observational registry including all the Florence area residents who experienced AMI from March 1, 2000 to February 28, 2001 and were admitted to hospital within 24 hours from symptom onset. Florence area includes 7 hospitals, 5 without the facilities to perform P-PTCA and 2 with specific programs for P-PTCA. This analysis refers to the 462 pts with ST-elevation AMI included in the registry who underwent P-PTCA.

Results: Of these pts, 281 (60.8%)were treated with ABC (bolus followed by 12 h infusion) and 181 (39.2%) were not. The corresponding rates of stent use were 96.4% vs 95.4%; TIMI 3 flow was restored in 99.3% vs 96.4%. At multivariate analysis, factors positively associated with ABC use were admission to a hospital with P-PTCA facilities (OR 2.2, 95%CI 1.4-3.3) and history of angina (OR 1.5, 95%CI 1.1-1.9), while factors associated with no ABC treatment were age as a continuous variable (OR 0.97, 95%CI 0.96-0.99) and AMI location other than anterior (OR 0.58, 95%CI 0.38-0.88); pts in Killip class > 1 were less likely to receive ABC (OR 0.53, 95%CI 0.32-0.88). In-hospital mortality was 2.5% in ABC-treated patients and 13.3% in the others (p<0.001). At multivariate analysis determinants of in-hospital mortality were age as a continuous variable (OR 1.11, CI 1.06-1.18) and Killip class > 1 (OR 3.9, CI 1.5-9.8). ABC treatment was associated with reduced mortality (OR 0.36, CI 0.13-0.99). In-hospital reinfarction and re-PTCA were 10.3% in ABC-treated pts and 8.8% in the others (p=0.60). Left ventricular ejection fraction of the pts alive at discharge was the same in the 2 groups (mean 45±12%).

Conclusion: Patients admitted to hospitals with P-PTCA facilities are more likely to receive ABC treatment. The reduced mortality observed in ABC-treated patients depends on their more favourable risk profile, even if an independent effect of ABC use is also suggested.

P1781 Facilitated percutaneous coronary interventions in patients with acute myocardial infarction transferred from remote hospitals

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Primary percutaneous coronary intervention (PCI) is a preferred therapy for myocardial infarction (MI) in centers having access to immediate invasive treatment but is frequently inaccessible to the community hospitals without catheterization facilities. We studied the safety and efficacy of facilitated PCI in patients (pts) with acute MI transferred from remote hospitals to catheterization facilities.

Methods: 200 pts with MI admitted to remote hospitals were enrolled if they presented within 12 hrs of chest pain onset, were eligible for thrombolysis and if the anticipated transfer time to catheterization laboratory was > 90 min. All pts received i.v. bolus of 60U/kg heparin, 15 mg alteplase and 0.25 mg/kg abciximab at the remote hospital and were immediately transferred to angiography. Infusion of alteplase (35mg/60 min) and abciximab (0.125 ug/kg/min) was continued during transfer.

Results: Average transport time was 97±39 min, and remote hospital door to needle time was 158±61 min. No death, and one ventricular fibrillation occurred during transportation. Mean time from lytic therapy administration to angiography was 124±39 min. In baseline angiography TIMI 3 flow was present in 71%, and patent infarct related artery (TIMI 3+2) was found in 86% of pts. Immediate PCI was performed in 150 pts with 92% procedural success rate. Corrected TIMI frame count before PCI was 35±30 and after PCI decreased to 20±13. In 42% of pts TIMI Myocardial Perfusion Grade (MPG) 3, and in 26% of pts MPG2 was achieved after PCI. The frequency of adverse cardiovascular events in the 30-day follow-up was rather low with 3.5% mortality rate, 1% recurrent MI, 1.5% repeat PCI and 1% intracranial bleeding. However, there were also 3% severe, 1.5% moderate and 14% mild bleeding complications.

Conclusions: Transferring patients from remote (>90 min. transfer time) hospitals to angioplasty center after administration of combined lytic and IIb/IIIa blocker therapy was feasible and safe. This combined therapy resulted in 71% TIMI 3 flow and opened infarct related artery in 86% of pts before PCI. Patients after such combined lytic therapy could undergo immediate PCI procedure (facilitated PCI) with high procedural success rate. However, bleeding complications occurred with rather high frequency.

P1782 Effect of stent-implantation versus balloon angioplasty on blood thrombogenicity in patients with acute myocarial infarction

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Background: Activated platelets are an independent predictor for thrombotic events after percutanous coronary intervention and stent implantation. Newer trials point to the benefit of early platelet inhibition and blockade of platelet-leukocyte interaction for prevention of coronary thrombosis. Our study examined platelet-leukocyte interaction and platelet activation in blood in patients with acute myocardial infarction (AMI) randomised to stent-implantation versus balloon angioplasty.
Methods and Results: 57 patients with AMI were included into our study. Patients were excluded when receiving fibrinolytic agents or GP IIb/IIIa receptor antagonists. All patients were treated with heparin, ticlopidine (250 mg BID) and aspirin (100 mg). Blood samples were taken from a peripheral vein before, immediately after intervention and after 24 hours and analysed by flow cytometry. Platelet-leukocyte aggregates in blood were comparable before intervention in patients randomised to stent-implantation (n=31) or balloon angioplasty (n=26) (3,9% (2,8; 4,7) versus 4,05% (3,4; 4,5)). Patients with implantation of a heparin-coated coiled wire stent showed a significant decrease in platelet-leukocyte aggregates 24 hours after intervention (3,9% (2,8; 4,7) versus 3,2% (2,4; 4,1); $p < 0,01$). No difference in platelet-leukocyte aggregation was found in patients treated with balloon angioplasty only. Platelet activation was increased immediately after intervention in both groups.
Conclusion: An inhibitory effect of stent-implantation on platelet-leukocyte aggregation in blood was demonstrated in patients with AMI. Passivation of the vessel wall and removal of the dissection-membrane by the stent reduces platelet-leukocyte interaction in the circulation and may relate to the clinical benefit of stenting in AMI.

P1783 Comparison of Culprit lesion targeting versus multi lesion trageting for primary and early percutaneous coronary intervention in acute myocardial infarction

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Treatment of acute myocardial infarction (AMI) has undergone dramatic changes due to new interventional techniques and improved thrombolytic agents. Primary PCI, especially stenting of the culprit lesion under GPIIb/IIIa blockade, is a world wide accepted approach. A certain amount of patients suffering from AMI have multi-vessel coronary artery disease with several other high-grade stenosis beside the culprit lesion (cpl). There is very limited data on patient 's outcome after PCI targeting the cpl alone compared to targeting of additional lesions beside the cpl.
Between January 1st 1999 and February 1st 2002 346/346 patients underwent diagnostic and 288/346 immediate therapeutic cardiac catheterization for treatment of AMI. 58/346 patients were either transferred for CABG, underwent PCI later or had no significant stenosis. 1-vessel-disease was present in 82/288, 2-vessel-disease in 100/288 and 3-vessel disease in 103/288 patients. PCI of the cpl alone was performed in 191/288 patients and 97/288 underwent multiple interventions. Overall inhospital mortality was 12/288 patients (4.1%) undergoing PCI and additional non-fatal MACE occurred in 11/288 patients (3.8%).
No significant difference concerning mortality, occurrence of non-fatal MACE and duration of hospitalisation was found in comparison of the 6 groups presented in the table. Patients were divided into the 6 groups according to the targeted lesions (Cpl= intervention of the culprit lesion, IRA= intervention of an additional lesion in the infarct related artery (IRA), non-IRA= intervention of an additional lesion located in an artery not related to the acute MI).

Affected vessels	Procedures (n)	Location of intervention	Patients (n)	Hospital days	Death n (%)	MACE n (%)	Level of significance
1	1	Cpl	62	5.0	1 (1.6)	2 (3.2)	n.s.
1	>1	Cpl + IRA	20	5.3	0	0	n.s.
2	1	Cpl	66	5.7	5 (7.6)	1 (1.5)	n.s.
2	>1	Cpl + IRA/non-IRA	34	6.1	1 (2.9)	1 (2.9)	n.s.
3	1	Cpl	63	6.9	3 (4.8)	4 (6.4)	n.s.
3	>1	Cpl + IRA/non-IRA	43	5.9	2 (4.7)	3 (6.9)	n.s.

We conclude that complex interventional coronary r revascularisation in AMI is safe and effective. Randomised trials including a larger number of patients are warranted to verify our experience.

P1784 Reduction of coronary blood flow during early phase of reperfusion as a predictor of microvascular injury during acute myocardial infarction

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In acute myocardial infarction (AMI), recanalization of the infarct related artery (IRA) with primary angioplasty leads usually to restoration of epicardial blood flow. This, however, may not translate into appropriate perfusion, since hypoxia and reperfusion impair coronary microcirculation and induce cardiac myocyte damage. The aim of the study was to estimate the relation between dynamic changes of coronary blood flow in IRA during the early phase of reperfusion and microvascular injury in 272 consecutive patients (pts) with AMI (mean age 54.7±10.5 years) treated with primary angioplasty in our institution.
The pts were divided into two groups: reflow (TIMI-3) and no-reflow (TIMI<3). ECG (total ST elevation in all leads, [tST]) and hemodynamic status (heart rate [HR]/systolic blood pressure [SP]) were collected before [B], straight after completion of the procedure [C] and 24 hours later [C24]. Coronary flow (TIMI scale and corrected TIMI frame count, CTFC) was evaluated at the above time points and, in addition, immediately after opening of the IRA [O]. Microvascular injury was assessed by (i) regression of ST segment elevation (tST-C/tST-B and tST-C24/tST-B); (ii) maximal CK-MB release (iii) HR/SP-B, HR/SP-C, HR/SP-C24. Coronary flow impairment (CTFC-red [frame]) was defined as the difference between CTFC-C and CTFC-O.
TIMI-3 flow was achieved in 236 pts [90,8%] immediately after IRA opening. In the early phase of acute reperfusion (6-30 min, on average 12.6 min), between IRA opening and end of PCI we found a reduction in TIMI flow by at least 1 point in 19 pts. Thus, at the end of PCI 224 (86,2%) pts had TIMI-3 flow, whereas in 19 (13,8%) pts the no-reflow phenomenon (TIMI<3) occurred.
CTFC-C was bigger than CTFC-O in group reflow (18,98±6,92 vs. 21,04±7,48; p=0,03) and in group no-reflow (43,44±26,94 vs. 89,84±47,86; p=0,004). CTFC-red in the reflow group was 2,02±6,28 and in the no-reflow group was 46,34±42,82 (p<0,001). CTFC-red in groups with LAD vs. non-LAD IRA was 3,74±4,86 vs. 1,44±6,74 (p=0,041). CTFC-red correlates with tST-C/tST-B (r=0,52, p<0,001), tST-C24/tST-B (r=0,59, p<0,001), maximal CK-MB (r=0,35, p=0,001) and HR/RR-C24 (r=0,44, p<0,001).
Conclusions: 1.In patients with AMI treated by primary angioplasty, successful IRA opening is usually followed by a subsequent reduction in coronary flow in the early phase of reperfusion.
2.The reduction in coronary flow correlates with microvascular injury.
3.Our data indicate that the reduction in IRA flow following successful IRA opening may be a clinically useful early indicator of microvascular injury.

P1785 Intracoronary localregional delivery of abciximab over a 3 French catheter in acute myocardial infarction

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Background: In acute myocardial infarction a subset of patients treated with primary angioplasty maintained an occluded vessel even after multiple dilatations. In these cases of occlusive intracoronary thrombi the systemic application of platelet glycoprotein IIb/IIIa antagonists could not reach the small vessels distal of the stenosis and restore the flow in the microcirculation. We evaluated the localregional delivery of abciximab. The drug was injected through a 3 French (F) multipurpose catheter directly into the distal coronary vessel.
Methods: From June 1999 until July 2001 we performed primary angioplasty at 208 consecutive patients with acute myocardial infarction. We could restore a TIMI 3 flow in 188 patients with balloon dilatation and if necessary with systemic application of abciximab. In 20 (9,6%) cases we found even after repeated balloon angioplasty a thrombotic occlusion or a slow flow (TIMI 0-2). The average age of these patients was 63,4 years, 14 (70%) were males and 5 (26%) of them had undergone a prior bypass operation. Half of the dose of abciximab was given through the guiding catheter and the other half through a 3 F catheter distal of the stenosis. All patients received a stent and were treated with additional acetylsalicyclic acid and clopidogrel.
Results: After localregional delivery of abciximab and balloon angioplasty in 18 of 20 cases (90%) a TIMI 3 flow could be restored, in the other 2 (10%) a TIMI 2 flow was achieved. On average it lasted 40.9 minutes (15 to 82 minutes) from the beginning of the procedure to the time the blood flow was restored. The maximum of the creatinine kinase was 1218 U/l on average. One patient died 13 days after the infarction in cardiogenic shock. After 6 months the angina classification was CCS I of 18 patients on average (one non related death). 16 patients were event free, one patient needed coronary bypass grafting and one other had a myocardial infarction. The left ventricular ejection fraction rose from 43,7% at discharge to 55,7% in 6 months after the therapy.
Conclusion: The intracoronary localregional delivery of abciximab restored blood flow in the infarct related vessel in a high percentage. The TIMI 3 rates (90%) and the 6 months clinical results encourage the use of localregional application of abciximab in occluded vessels to improve microvascular circulation.

P1786 Improved myocardial salvage with gradual reperfusion angioplasty compared to coronary stenting for acute anterior myocardial infarction

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Experimental studies indicate that staged reperfusion plays a role for restoration of reperfusion injury in occluded coronary artery. We sought to evaluate the impact of gradual reperfusion angioplasty to coronary stenting in patients with acute myocardial infarction (AMI). We performed a prospective analysis of 127 patients with anterior AMI. Prolonged (10 minute) dilatations were performed in 40 patients using perfusion balloon (GRA), 43 patients delivered coronary stenting (SRA), and the other 44 patients received standard (1 minute) dilatations using standard balloon (BRA). GRA group had a less ST re-elevation (GRA30%, SRA67%, and BRA64%; $p<0.05$) and a lower rate of major arrhythmia (15%, 46%, and 45%; $p<0.05$) in the acute phase. Regional wall motion improved significantly over the baseline (-2.65 SD/chord) at the time of AMI when seen at 1 month (-2.35, p=0.048) and 6 months (-2.20, p=0.047), and 3 years (-2.12, p=0.045) after the infarction in GRA group, which was not observed in SRA and BRA groups. At 3-year follow-up, the rate of target vessel revascularization was 27.3%, 23.3% and 47.7%, respectively (p=0.035). Mismatch of thallium-201 and fatty acid metabolism imagings was 33.0%, 15.1%, 11.8%, respectively (p=0.042). Major adverse cardiac events occurred less frequently in GRA group (0%, 11.6%, 2.3%: p=0.028). Gradual reperfusion angioplasty may prevent reperfusion syndrome and ventricular remodeling in AMI, reducing cardiovascular events for a long term.

P1787 Direct coronary angioplasty of non-protected left main coronary artery in acute myocardial infarction

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Background: Although acute myocardial infarction (AMI) of left main coronary artery (LMCA) is a rare clinical entity, it carries a very high mortality rate.
Methods and Results: To evaluate the effect of balloon angioplasty (BA) and stenting in those patients (pts), data bank of 2195 AMI pts admitted in Kokura Memorial Hospital between January 1992 and December 2000 was searched. Emergency angiography showed LMCA obstruction in 38 pts (1.7%), and all of them received direct BA and needed IABP support to prevent development of cardiogenic shock. Of the 38 pts, 17 pts (45%) discharged alive and in-hospital death occurred in 21 pts (55%).
Successful reperfusion rate was significantly higher in survived pts than in died pts (17/17, or 100% VS 12/21, or 57%; $p<0.01$). Use of PCPS (18% VS 57%), time from onset to angioplasty (3.7±2.8 hrs VS 2.3±1.6 hrs), and incidence of emergency CABG (35% VS 14%) had no significant difference between survived and died pts. Survived pts were less likely to have cardiogenic shock (10/17, or 59% VS 20/21, 95%; $P<0.01$). On arrival to emergency room, base excess (BE) and pH were higher in survived pts than in died pts; BE: -4.3±4.0 mmol/l VS -11.0±6.3 mmol/l ($p<0.001$), pH: 7.40±0.10 VS 7.29±0.15 ($p<0.01$). Stent implantation in LMCA was subsequently attempted after BA in 26 pts (68%). Reocclusion of LMCA occurred in 2 pts (17%) of 12 non-stented pts and in none of 26 stented pts; $p<0.05$.
Conclusions: 1) Mortality rate of LMCA-AMI is high, especially complicated by cardiogenic shock. 2) To achieve successful reperfusion by direct angioplasty is an indispensable condition requisite for survival. 3) Prognosis on LMCA-AMI would be associated with hemodynamic changes on admission due to cardiogenic shock. 4) Stenting is effective to prevent reocclusion.

P1788 Long-term outcome in patients with early restrictive filling pattern after anterior acute myocardial infarction treated with primary PTCA

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Background: Preliminary studies have shown that patients with a restrictive left ventricular (LV) filling pattern early after acute myocardial infarction (AMI) had a poor outcome at medium follow-up even if successfully treated with primary percutaneous angioplasty (PTCA). However, information about the long-term impact of restrictive LV filling pattern in this clinical setting are still missing.
Objective: We sought to assess the long-term outcome in patients with restrictive LV filling pattern early after a first anterior AMI successfully treated with PTCA.
Methods: In 104 patients, two-dimensional and Doppler echocardiograms were obtained three days after the index AMI. Coronary angiography was performed in all patients at six months after PTCA. The patients were classified into two groups according to the Doppler-derived mitral deceleration time (DT): group 1 (n = 34) with DT $\leq$ 130 msec (restrictive filling pattern) and group 2 (n = 70 patients) with DT > 130 msec (non-restrictive filling pattern). All patients were followed-up for a mean (± SD) period of 53 ± 15 months.
Results: The 6-month coronary patency rate was similar (92%) in both groups. During the follow-up period, 17 patients (16.5%) were admitted to the hospital for congestive heart failure, 14 (41%) in the group 1 and 7 (10%) in the group 2 ($p < 0.001$), and 12 patients (11,5%) died, 9 (26%) in group 1 and 3 (4%) in group 2 ($p < 0.001$). Re-infarction occurred in 1 patients in both groups (3% vs 1%, p= 0.598). The survival rate and the event-free survival rate at mean follow-up were 74% vs 96% ($p < 0.001$) and 44% vs 94% ($p < 0.001$), respectively. Finally, in the survived patients the NYHA class was significantly higher in the restrictive group that in the non-restrictive group (2.1 ± 0.9 vs 1.4 ± 0.6, $p < 0.001$).
Conclusion: Patients with a restrictive LV filling pattern early after a first anterior infarction successfully treated with primary PTCA have a poor clinical long-term outcome.

P1789 Relations of myocardial viability to coronary flow reserve after anterior myocardial infarction treated with PTCA

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Objective: To assess the relationship of myocardial viability to coronary flow reserve evaluated by transthoracic echocardiography in the infarct-related coronary artery after anterior myocardial infarction (AMI) treated with primary PTCA.
Methods: 54 patients with AMI (mean age 64±11 years, 72% males) were treated with primary PTCA (latency 4±3 hours) and underwent dobutamine stress echocardiography (DSE) and coronary flow reserve (CFR) study within three months of the acute event. Under continuous electrocardiographic and echocardiographic monitoring, dobutamine was administered in incremental doses of 5, 10, 20, 30 and 40 μg/kg/min, the first two stages lasting 5 minutes (low doses, LD), the others 3 minutes (high doses, HD), adding atropine when 85% of predicted maximal heart rate (endpoint) was not attained. Presence of positive ischemic response or occurrence of arrhythmias, hypotension, abnormal pressure increase, were all criteria for premature DSE test interruption, prior to endpoint. In 37 patients, CFR was assessed as the ratio of diastolic peak velocity after adenosine infusion (140 μg/kg/min for 5 minutes) to baseline diastolic peak velocity in the distal left anterior descending coronary artery, visualized by trans-thoracic echocardiography with contrast enhancement. Left ventricular (LV) wall motion score index (WMSI) was calculated on 16 segments (1=normal motion; 2 hypo-, 3 a-, 4 dys-kinesia; 5=aneurysm).
Results: baseline WMSI correlated positively with enzymatic peak values and LV volumes, and negatively with LV ejection fraction; changes in WMSI indicated some myocardial viability within necrotic area, with minimal ischemic response (infarct area WMSI: baseline 2.4±0.5, LD 2.1±0.6, HD 2.2±0.6). CFR (1.9±0.4) correlated negatively with LV end-diastolic and end-systolic volumes (r=-0.36 and r=-0.48, respectively) and positively to ejection fraction (r=0.55)(all $p<0.05$); CFR was also negatively related to WMSI at all DSE stages (r=-0.30 at baseline, r=-0.46 at LD, and r=-0.41 at HD) and positively with WMSI changes from baseline DSE to LD (r=0.48, all $p<0.05$).
Conclusions: in AMI survivors treated with primary PTCA, the presence of viable myocardium within infarct area correlates positively with CFR in the infarct-related artery. Early revascularization appears to contribute to less severe myocardial ischemic injury and to preserve CFR, with a favorable impact on LV geometry and systolic function. This is suggested by the positive correlation of CFR to smaller LV dimensions and better systolic function.

P1790 Corrected TIMI frame count does not assess microvascular injury in patients with acute myocardial infarction after primary coronary angioplasty

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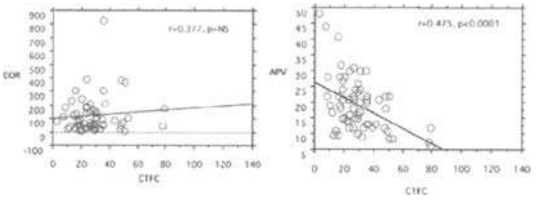
Objectives: The aim of this study was to evaluate the corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (CTFC) as a predictor of microvascular injury of the coronary bed in patients with acute myocardial function (AMI).
Background: Some studies have shown that average systolic peak velocity (ASPV) and diastolic deceleration rate (DDR), measured by using a Doppler guidewire, predict the degree of microvascular injury of the coronary bed.
Methods and Results: We measured CTFC and coronary flow velocity immediately after primary coronary angioplasty in 71 patients with anterior AMI. CTFC correlated with average peak velocity (APV) (r=0.475; p<0.0001). However, there was no significant correlation with DDR (r=0.145; p=NS) or ASPV (r=0.377, p=NS).



Comparison of DDR & APV with CTFC.

Conclusions: Although CTFC reflects coronary flow velocity, it is not accurate enough to assess the degree of microvascular injury after primary coronary angioplasty.

INTERVENTIONS AFTER MYOCARDIAL INFARCTION

P1791 TIMI myocardial perfusion grade (TMPG) correlates with myocardial salvage in patients with acute myocardial infarction treated with thrombolysis and stenting

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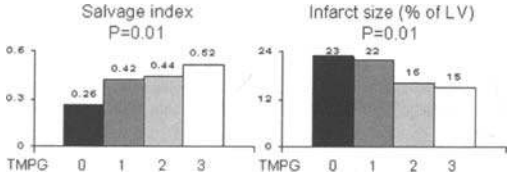
TMPG has recently been introduced as an angiographic index of myocardial perfusion. In recent studies, it has been associated with mortality and infarct size after thrombolysis for acute myocardial infarction (AMI). Its relationship to myocardial salvage as assessed by single photon emission computed tomography after thrombolysis or stenting for AMI has not been examined.
We studied the relationship of TMPG to myocardial salvage and infarct size in 248 patients (pts) enrolled in the randomized STOPAMI 1 and STOPAMI 2 trials. These trials compared stenting with thrombolysis in pts with AMI. Area at risk was measured by scintigraphy at baseline. Final infarct size was measured by a second scintigraphy at 1-2 weeks after randomization. Salvage index was calculated as the proportion of area at risk salvaged by reperfusion. Pts of both interventional and thrombolytic arms were scheduled for coronary angiography at 1-2 weeks after randomization. TMPG was assessed according to the definition of Gibson et al (Circulation 2000; 101:125-130).
There were 52 pts with TMPG 0, 47 pts with TMPG 1, 59 pts with TMPG 2 and 90 pts with TMPG 3. They did not differ with respect to the area at risk (p>0.3). The analysis showed that TMPG was significantly related to salvage index and infarct size: the higher the TMPG the greater the salvage index and the smaller the infarct size. In the multivariate analysis, the relation between TMPG and salvage index was independent from the form of reperfusion therapy.



Conclusions: These results confirm previous findings on the relationship between TMPG and final infarct size. In addition, our study shows that TMPG is a useful marker of the degree of myocardial salvage achieved with intervention or thrombolysis.

P1792 One-year benefitial effect of stenting in anterior acute myocardial infarction due to proximal LAD occlusion. Results from the CADILLAC trial

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Among patients with anterior MI, those with proximal LAD occlusion have a poorer prognosis. Whether stenting is of benefit in this subset is still under debate. This issue has been analysed from the data obtaines in the CADILLAC study.
The multicenter international CADILLAC trial included 2082 AMI patients treated with primary PTCA, that were randomized to 4 different strategies: balloon, balloon plus abciximab, stent and stent plus abciximab. Out of the 2082 patients, 441 (21.2%) presented a proximal LAD infarction, this subset comprising the study group. Of them, 224 (50.8%) were treated with balloon and 217 (48.2%) were asigned to stent implantation.
Results: Table shows differences in outcome between patients randomized to balloon or stent.

Ballon vs stent in prox LAD infarction

	Balloon	Stent	p
MACE at 30 days	15 (5.8%)	18 (8.3%)	0.305
Death	6 (2.7%)	11 (5.1%)	0.190
Disabling stroke	0	0	
Re-MI	1 (0.5%)	3 (1.4%)	0.365
Ischemic TVR	7 (3.1%)	6 (2.8%)	0.823
CABG	1 (0.5%)	3 (1.4%)	0.365
PCI	6 (2.7%)	3 (1.4%)	0.504
Severe bleeding	0	1 (0.5%)	0.492
MACE at 1 year	53 (23.7%)	40 (18.4%)	0.178
Death	12 (5.4%)	18 (8.35)	0.219
Disabling stroke	0	0	
Re-MI	8 (3.4%)	8 (3.4%)	0.948
Ischemic TVR	41 (18.3%)	19 (8.8%)	0.003
CABG	8 (3.4%)	7 (3.2%)	0.841
PCI	33 (14.7%)	12 (5.5%)	0.001
SAT	5 (2.2%)	1 (0.5%)	0.216

Conclusion: In patients with anterior MI secondary to proximal LAD occlusion, coronary stenting is associated with a 52% reduction in the rate of ischemia driven TVR at 1 year. Stent implantation in this subset should be considered mandatory when possible.

P1793 Determinants of transferral to a hospital with invasive facilities and outcome in acute myocardial infarction patients first admitted to community hospitals

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Background: Primary PTCA (P-PTCA) is an effective reperfusion treatment in patients (pts) with acute myocardial infarction (AMI), but this technique can hardly be widespread to community hospitals (CH). In pts first admitted to CH, the appropriateness of transferring criteria to tertiary centres with invasive facilities may be a relevant determinant of outcome.
Methods: The AMI-Florence Registry is a prospective observational registry including all the Florence area residents who experienced AMI from March 1, 2000 to February 28, 2001. This analysis refers to the 539 pts with ST-elevation AMI included in the registry who were admitted to the 5 CH of the Florence area without P-PTCA facilities.
Results: Of these pts, 377 (70%) were treated locally (11.4% with thrombolysis) (Group 1), and 162 (30%) were transferred to centres with P-PTCA facilities (Group 2). According to univariate analysis, Group 1 pts were older (age 74.1 ± 12.4 vs. 68.1 ± 12.6 years, p<0.001), had more frequently AMI other than anterior (77.7% vs. 53.0%, p<0.000), previous heart failure (16.2% vs. 3.1%, p<0.000)and were more frequently in Killip class >1 at admission (40.3% vs. 25.9% p=0.006). According to multivariate analysis, the variables negatively associated with transferral to a tertiary hospital were older age as a continuous variable (OR 0.98, 95%CI 0.96-0.99), AMI other than anterior (OR 0.26, 95%CI 0.17-0.41) and previous heart failure (OR 0.28, 95%CI 0.11-0.75). The history of angina (<1 month) was the only factor positively associated with transferral (OR 2.30, 95%CI 1.41-3.75). In-hospital and 6-month mortality was 14.3% and 25.2% in Group 1 vs 6.2% and 12.4% in Group 2 (p=0.007 and p=0.001, respectively).
Conclusion: Older and more severe pts were less likely to be transferred from CH to tertiary hospitals to undergo P-PTCA. These data rise doubts about the appropriateness of the used transferring criteria.

P1794 Outcome of elderly patients with acute myocardial infarction complicated by cardiogenic shock undergoing routine early coronary revascularization

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Background: The Shock Trial did not show any benefit of an early invasive strategy in elderly patients (pts) with acute myocardial infarction (AMI) complicated by cardiogenic shock (CS). Morever, elderly pts with cardiogenic shock are poorly represented in the Shock Trial and in several Registries of CS.
Methods: Analysis of the outcome of pts aged > 75 with AMI complicated by cardiogenic shock.
Results: Out of 205 pts with cardiogenic shock, 71 were aged > 75, and 134 were younger than 75 years. There was a greater incidence of women in the elderly group (51% vs 20%, p<0.001), while there were no differences between groups in the other baseline variables. The primary procedural success rates were indentical for the two groups (96%), and most pts had primary coronary stenting. The six-month mortality rate was 51% for elderly and 25% for younger pts (p<0.001). Multivariate analysis showed age (OR 1.07, 95% CI 1.04- 1.09), multivessel disease (OR 1.90, 95% CI 1.06-3.39) and anterior AMI (OR 1.90, 95% CI 1.05-3.46) to be independent predictors of mortality.
Conclusion: Age is a strong predictor of mortality in pts with cardiogenic shock after successful early coronary revascularization. However, the six-month survival of 49% in this high risk subset of pts suggests that the benefit of an early revascularization strategy persits also in elderly pts.

P1795 Safety of early transferring of thrombolysed patients with ST-segment elevated acute myocardial infarction to undergo coronary intervention: results from the GRACIA trial

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Background: Because of the efficacy of stenting in achieving a stable normal flow, coronary interventions performed immediately or hours after thrombolysis grow sharply. However, safety of transportation during recent or ongoing reperfusion remains undetermined.
Methods: The GRACIA trial included 500 pts randomly assigned to angiography and intervention within 24 hours of thrombolysis, or conservative posthrombolysis ischemia-guided approach. Interventional arm of this trial included 189 pts admitted and randomised in tertiary hospitals and 61 pts admitted in hospitals without interventional facilities, who needed posthrombolysis ambulance transferring to undergo coronary intervention. To assess the safety and feasibility of early posthrombolysis transferring, we compared the outcome of interventional transferred (n=61) and non-transferred patients (n=189). Travel distance was 34.9±35 Km. Transportation lasted 29±19 minutes. In 92% of cases pts were accompanied by well trained paramedics and a physician from the referring hospital.
Results: There were no differences between transferred and non-transferred pts in terms of clinical profile and infarct characteristics. Time delay between thrombolysis and angiography was longer among transferred pts (881±452 min vs 697±532 min, p=0.01). There was only one event (angina) during transportation (1.6%). Incidence of cardiac events from thrombolysis to angiography was similar in both groups (transferred: 20% non-transferred: 13%, p=0.22) and no patient died during this period. Bradycardia was more frequent among transferred patients (13 vs 5%, p= 0.05), but the incidence of ventricular tachycardia or fibrillation was similar in both groups (transferred: 1.6%; non-transferred: 3%, p= 0.85)
Conclusions: In the setting of AMI with ST segment elevation recently thrombolysed, ambulance transportation of patients to undergo complementary coronary interventions is feasible and safe.

P1796 Left ventricular remodelling after first anterior wall myocardial infarction: effect of delayed angioplasty (a new aspect for an old theory)

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Background: The concept that a patent infarct related artery (IRA) and myocardial reperfusion confer a benefit beyond that resulting from myocardial salvage has given rise to the "open artery theory" which now receives a considerable support.
Aim of this work is to evaluate the effect of delayed (within one month after AMI) percutaneous coronary interventional (PCI) revascularization procedure on LV remodeling after first anterior wall Q-wave acute myocardial infarction (AMI).
Patients and methods: A total of 80 patients, with first anterior AMI and <2 TIMI flow grade of the IRA, were selected and divided into: group A (40 patients) received, in addition to their conventional medical treatment, a PCI within one month after AMI and group B who received, only, the conventional medical treatment.. Left ventricular remodeling was assessed by echocardiography by measuring the end-diastolic (EDVI) and end-systolic volume indices (ESVI), resting wall motion scoring index, and LV ejection fraction (EF). These variables were measured as baseline, one, three and six months after AMI in both groups. Follow up coronary arteriography was done for all patients in the intervention group at the end of the six–month study to exclude patients in whom restenosis occurred.
Results At the 3-month study, ESVI and WMSI were significantly less in group A than group B (ESVI: 46.18±15.16 versus 49.95±12.42 ml3/m^2, p value <0.05, and WMSI: 1.28±0.17 versus 1.39±0.19, p<0.01, for group A and B respectively). At the 6-month the EDVI, ESVI and WMSI were significantly less in group A as compared to group B (EDVI: 132±25 versus 146±25.5 ml3/m^2, p<0.05 and ESVI: 43±13.8 versus 54±14.6 ml3/m^2, p<0.01, WMSI: 1.27±0.16 versus 1.46±0.21, p<0.01, in group A and B respectively. Global EF% increased significantly in group A as compared to group B (64.8±5.7 versus 56±6.8%, p<0.01).
Conclusion: These findings suggest that delayed PCI can reduce left ventricular remodeling after acute anterior wall myocardial infarction. The present study may serve as a basis for a large prospective mortality trial on this important issue

P1797 Outcome of elective percutaneous coronary interventions in ASSENT-3

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Background When compared with unfractionated heparin (UFH), co-therapy with enoxaparin (ENOX) or abciximab (ABC) results in a reduction of ischaemic complications after ST-elevation acute myocardial infarction (AMI) treated with TNK-tPA (ASSENT-3; n=6095). The effect of these new co-therapies on clinical outcomes in patients undergoing an elective percutaneous coronary intervention (PCI) after the acute event is not known.
Methods Clinical outcomes in patients undergoing elective PCI early after AMI in the ASSENT-3 trial (n=1064; 17.5% of total study population) were compared.
Results A similar number of patients underwent an elective PCI in the 3 treatment arms. The results are shown in the table.

Endpoints	UFH (n=332)	ENOX (n=348)	ABC (n=384)	P-value
Median time to PCI (days)	5	5	5	0.76
Primary efficacy endpoint *	22 (6.63%)	15 (4.31%)	20 (5.21%)	0.41
30-day mortality	4 (1.20%)	2 (0.57%)	6 (1.56%)	0.42
In-hospital myocardial reinfarction	10 (3.01%)	5 (1.44%)	6 (1.56%)	0.28
Reinfarction after PCI	5 (1.51%)	2 (0.57%)	2 (0.52%)	0.32
In-hospital refractory ischaemia	10 (3.01%)	9 (2.59%)	9 (2.34%)	0.86
Intracranial haemorrhage (ICH)	1 (0.30%)	1 (0.29%)	0 (0.00%)	0.41
In-hospital major bleeds (excl. ICH)	10 (3.01%)	7 (2.01%)	11 (2.86%)	0.66
Major bleed at arterial puncture site	3 (0.90%)	3 (0.86%)	2 (0.52%)	0.80
Minor bleed at arterial puncture site	35 (10.54%)	31 (8.91%)	36 (9.38%)	0.76

* Primary efficacy endpoint of ASSENT-3: 30-day mortality + in-hospital myocardial reinfarction + in-hospital refractory ischaemia; P-value: likelihood ratio test for overall difference between treatment groups

Conclusions In this post-hoc analysis of the ASSENT-3 trial, clinical outcomes in patients undergoing an elective PCI early after AMI were similar in the 3 treatment arms with a trend towards fewer efficacy endpoints in the ENOX and ABC arms. No excess of bleeding complications was observed after co-therapy with ENOX or ABC when compared with UFH.

P1798 Reperfusion block: the availability of primary PTCA does not increase the percentage of myocardial infarction patients receiving reperfusion therapy

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Background: The current guidelines recommend the use of thrombolytic treatment in patients with acute myocardial infarction (AMI) who present to the hospital within 12 hours of symptom onset. For patients with contraindications to thrombolytic treatment or who are at increased risk of bleeding, primary angioplasty is recommended. We hypothesized that the increasing number of cath labs and the availability of primary PTCA in Israel would render an increase in the % of MI patients treated with reperfusion therapy.

Methods and Results: We analyzed data obtained from 4 national surveys conducted in all CCUs in Israel from 1992 to 2000. In the last survey (2000) 19 of the 26 CCUs had on-site cath labs.

Trends in Reperfusion 1992 to 2000

	1992 (n=941)	1996 (n=2386)	1998 (n=1076)	2000 (n=1244)	p for trend
Age (yrs)	63+13	63+13	64+12	63+13	0.05
Male %	75	74	74	77	0.55
ST > MI%	-	-	75	76	NA
Aspirin %	72	91	94	96	<0.001
Beta-block %	31	55	60	64	<0.001
ACE-inhib %	19	50	53	53	<0.001
Lysis %	44	49	42	38	<0.001
Prim PTCA %	-	4	6	10	<0.001
Reperfusion %	44	53	48	48	0.46
Angio	22	37	49	51	<0.001
Any PCI %	7	22	28	39	<0.001
Death 30d %	13.5	9.7	9.6	10.4	0.05
Death 1 yr %	19.3	14.2	15.1	NA	0.005

Conclusions: Over the last decade, the overall % of MI patients who received reperfusion therapy remained constant. The increased utilization of primary PCI was associated with a parallel decrease in the use of thrombolysis. The decline in MI mortality observed in the early 90's leveled off since the mid 90's. Further efforts are needed to expand the proportion of MI pts who receive reperfusion therapy. If successful, such efforts would lead to a renewed decline in MI mortality.

P1799 Percutaneous angioplasty for late opening of infarct related arteries: predictors of one year clinical outcome

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Background: The potential benefit of re-opening occluded infarct-related arteries (IRA) by percutaneous coronary intervention (PCI) is still debated. We assessed the immediate and long term clinical outcome of patients submitted to systematic attempt at IRA re-opening in a setting of a sub acute (>72 hours and <10 days) myocardial infarction (MI).

Methods and Results: 199 consecutive patients matching these criteria were submitted to PCI and followed up for one year. Three endpoints were defined: (1)=composite of death, new Q wave MI, peri-procedural creatine kinase (CK) release >3 times the upper limit of normal, stroke, major bleeding, or need for urgent revascularisation at 30 days; (2)=one year survival without stroke, new MI or unstable angina; and (3)=endpoint #2 plus need for target lesion revascularization. Re-opening of the IRA was successful 159/199 (80%) patients, with stent implantation in 99 (50%). Endpoint #1 occurred in 16 (8%) patients; endpoint #2 in 30 (15%) and endpoint (3) in 44 (22%). Two year event free probability was 0.75±0.05 and 0.72±0.04 for endpoints #2 and #3 respectively. Left ventricular ejection fraction (LVEF) (odds ratio = 0.86 [0.79;0.94], p=0.001 per additional percent of LVEF) and CK release (1.01 [1.00;1.01], p=0.04 per additional unit of CK released) were independent predictors for endpoint #2, with LVEF being the only independent predictor of endpoint #3. Lack of stent implantation (odds ratio = 0.28 [0.05;0.5], p=0.04) and CK release (1.01 [1.00;1.01], p=0.03) were independent predictors of death.

Conclusion: Clinical outcome of patients submitted to systematic attempts to re-open occluded IRA in the setting defined in this study is mostly influenced by post MI LV function. Peri-procedural enzyme leakage and lack of stent implantation negatively influence late clinical outcome.

P1800 The effect of revacularization rate on prognosis of high risk acute myocardial infarction patients. An OPTIMAAL substudy

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The effect of revascularization on prognosis in high risk post myocardial infarction (MI) pts, who were not candidates for initial interventional therapy, but with optimal medical therapy incuding ACE inhibitor or Angiotensin II blocker, has not been tested.

Material: Patients (pts) with MI (n= 5477)during initial hospitalization, with high risk profile including signs of heart failure or anterior MI with optimal medical therapy were included into analysis. Patients for whom immediate revascularization was planned were excluded from the study. Early revascularization was performed within 30 days in 550pts (10%, 398 PCI, 143 CABG and 9 had both) and within 360 days in total 1407 (25,7%, 789 PCI, 569 CABG and 49 had both procedures) of pts. The distribution of revascularization procedures at 1 year was uneven in this multinational population: Finland 28,1%, Denmark 29,3%, Norway 23,1%, Sweden 23,5%, UK 14% and Germany 38%. At baseline more patients were smokers in Denmark 42,1%, while in Germany 43,9% of pts had had previous PCI and with higher use of betablocking agents in Finland. There was no major difference in age, cholesterol, previous myocardial infarction or other characteristics.

Results: The mortality was reduced by revacsularizations in total study population by 48% (p< 0,0001), in PCI group by -50% (P<0,0001) and -40% by CABG (p<0,0001). In patients with lower EF (<35%) greater effect of revascularization on mortality is seen in PCI pts (52% lower) and in CABG pts (51% lower).

The reduction in mortality varied, with -74% decrease in Denmark, Finland -40%, concomitantly Norway -57%, Sweden -56%, UK -48%, Germany only -16% with highest revascularization rate. During up to 3 y follow-up the total death rate was 17%, while in Germany 12%.

Conclusion: These results suggest that revascularization either with PCI or CABG improves prognosis significantly in high risk patients after myocardial infarction.

Abstract P1801 – Table 1

IT % Change	<25% O	<25% OCC	25-50% O	25-50% OCC	>50% O	>50% OCC	Adj O	Adj OCC	Rem O	Rem OCC
MS	36.2±7.2*	19.8±5.4*	29.0±6.5*	25.6±4.8*	25.8±6.1	11.0±6.9	2.6±4.4	14.0±5.1#	-12.6±7.7	7.6±5.3#
Ecc	44.3±7.7*	25.8±6.0*	50.4±6.2*	39.0±5.4*	37.5±4.6	42.5±4.7	5.9±5.0	16.0±5.9#	-13.5±8.1	10.7±6.7#
Err	27.2±10.5*	-17.4±8.0*	267.0± 10.7*	-127.7±4.3*	81.9±2.4	101.9±4.4	108.3±7.9	-27.8±7.0#	13.5±11.2	2.3±10.4#
GLOBAL	O	OCC								
IS(g)	-6.9±40.6#	14.5±24.4								
EDV	-17.4±12.0#	27.2±24.9								
ESV	-27.4±14.9#	29.1±23.7								
EF	22.2±19.9#	-0.6±17.4								
LV Mass	-15.1±11.3#	0.3±9.5								

P1801 Effect of late recanalization for acute myocardial infarction on left ventricular remodelling. A prospective randomized study – Preliminary data

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Background: Clinical benefits of infarct related artery (IRA) recanalization later than 12h from symptoms onset(SO) after acute myocardial infarction (MI) still remain unclear.Objectives: We investigated whether IRA late recanalization would improve left ventricular(LV) remodeling at 6 months follow-up (FU).
Methods: We studied 12 anterior MI pts with: SO between 12h-14 days prior to enrollment(E), occluded(0CC) IRA (TIMI 0/1) on angiography, and no evidence of myocardial ischemia or viability on anterior wall by scintigraphy. The were randomized to either IRA recanalization by PTCA(O-6 pts) or no intervention (OCC-6 pts). Myocardial tagging and delayed-enhanced MRI were performed at E and FU. Infarct size (IS), LV end diastolic (EDV) and systolic volumes (ESV), ejection fraction (EF)and LV mass were measured. The influence of infarct transmurality (IT) on myocardial 2D strains (maximal shortening (MS), circumferential shortening (Ecc), radial thickening (Err)) were analized on infarcted, adjacent (Adj) and remote (Rem) LV segments.
Results are shown on table 1, where *p<0.05 (E vs. FU) and # p<0.05 (O vs. Occ). At FU, O had significantly better % MS, Ecc, Err when IT was <50%. No differences were found when IT was >50%. Adj and Rem segments had greater strains on OCC at FU.
Conclusion: This study demonstrates that late recanalization of IRA using PTCA improves LV remodeling and LV regional contractility over a period of 6 months. These findings support the open-artery hypothesis and may significantly impact clinical prognosis.

P1802 Single vessel versus multivessel revascularization for non-ST-segment elevation acute coronary syndromes in the elderly

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Outcome of patients submitted to PCI is heavily affected by advanced age and clinical instability. Moreover prevalence of multivessel disease in patients with acute coronary syndromes (ACS) increases with age.
Aim of the study is to compare immediate results and mid term outcome of lone culprit lesion revascularization versus multivessel PCI in over-75 years old pts. admitted for non ST elevation ACS.
Population and results: from October 1997 to August 2001 300 consecutive over-75 yrs old pts (mean age 78, range 75-91, age >80 (24%) underwent PTCA in our cath lab. A multivessel disease was present in 195 pts. (65%). In 137 pts. (70.2%) only the culprit vessel was treated (group A); at least two vessel were treated in 58 pts.(29.8%) (group B) during the same hospitalisation. Mean age, male to female ratio, left ventricular function, severity of angina (Braunwald classification), incidence of peripheral and cerebral vascular disease, diabetes, renal insufficiency, and procedure technique (number of stents, use of rotational atherectomy) as well as use of IIbIIIa inhibitors were not different in the two groups. LAD coronary artery was more frequently the culprit vessel in group B.
A procedural success was achieved in 98% of pts in both groups. During hospitalization in group A 1 Q wave MI (0.7%), 2 non-Q wave MI (1.4%), 1 stroke (0.7%), 10 (7.3%) vascular access complications were observed whereas in group B 2 pts died ((3.4%), 1 Q wave MI (1.7%), 3 non-Q wave MI (5%), 5 vascular access complications (8.6%). Follow up (4-24 months) was possible in all but two pts.: in group A 5 pts (3.8%) died; 1 Q wave MI (0.8%) and 1 non-Q wave MI were observed and 10 revascularization procedures (PCI or CABG) were performed (7.5%); in group B no death, 2 non-Q wave MI (3.4%) were observed and 3 coronary revascularization were performed (5%). Stable angina was present in 12 patients of group A (9%) and in 3 patients of group B (5%).
Conclusions: in elderly people with non ST elevation ACS and multivessel disease, PTCA of the culprit vessel respect to multivessel percutaneous revascularization is associated with a better immediate outcome but has an increased incidence of clinical events at follow up. Individual criteria such as quality of life and life expectancy and procedural difficulties should guide the choice between the two strategies of percutaneous revascularization.

P1803 The switch from conservative to invasive strategy in non-ST-segment elevation acute coronary syndromes in a peripheral coronary care unit; does it have a prognostic impact?

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Many landmark trials have discussed during the '90s the relative merits of the conservative and invasive strategies in the now called non-ST elevation acute coronary syndromes (ACS). A conservative approach has always been the initial choice in our Coronary Care Unit (CCU) without hemodynamic-interventional facilities and surgical back-up. Is this still clinically valuable and ethical? To investigate this item, we analyzed the short (30 days) and long (1 year) term prognosis of ACS patients (pts) admitted to our CCU from 1999 to 2001 (group A n=588) and historical controls from 1990 to 1992 (group B, n=534). Pts were matched (all p=n.s.) with respect to age (A 66+12 vs B 67+11 years), sex (males 75 vs 77%), previous myocardial infarction (MI) (14 vs 13.2%), diabetes (17 vs 18.1%), hypertension (48 vs 46.4%). Use of aspirin and nitrates did not differ; thrombolysis (12 vs 2%), i.v. heparin (86 vs 64%), calcium-channel blockers (74 vs 28%) had a higher use in group B (p<0.001), beta-blockers (43 vs 27%, p<0.001) and PCIs (4 vs 42%, p<0.0001) in group A, whose pts received also statins (87%), LMWHeparins (48%) and GP2b3a-ibitors (12%). Severity of angina, presence and entity of ST depression, younger age, Killip class >2 were indipendent predictors of PCIs, while troponins, 2-D echo data, previous MI were not. Group A had a shorter lenght of hospital stay (5.7 vs 7.8 days, p<0.01). At 30-day follow-up mortality (A 3.7 vs B 4.8%) and (re)MI (A 2.4 vs B 2.3%) did not differ (p=n.s.), while at 1-year follow-up group A had a lower mortality (7.2 vs 10.4%, p<0.01) and a tendency to lower (re)MI (4. vs 5.6%, =0.058). At multivariate analysis PCI (OR 0.57, 95%IC 0.43-0.88) was the most powerful predictor of improved survival, followed by beta-blockers (OR 0.74, 95%IC 0.56-0.99). In the daily experience of a medium-sized CCU the switch to a "primary" invasive strategy in ACS, associated to a careful secondary pharmacological prevention, has prognostic benefit and is cost-effective. Hemodynamic and interventional facilities should be extended, with the support of a "core" reference laboratory, in order to obtain a widespread optimization of ACS pts' therapy.

P1804 Randomized double blind study of percutaneous myocardial laser in chronic refractory angina

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Transmyocardial or percutaneous myocardial laser (PML) has been suggested to relieve symptoms in patients with chronic angina pectoris. However, the mechanism by which laser relieves symptoms is not known, and no previous study has been able to exclude a placebo effect. We included 82 patients into a double blind randomized study, of whom 40 underwent percutaneous myocardial laser (YAG: holmium) and 42 patients had a sham procedure. Statistical power calculation was based on improvement of CCS functional class. Among the 82 patients, 86.6% were in CCS class **III**, and 13.4% in class IV. The mean left ventricular ejection fraction was 64.7%, 82.9% of patients had triple vessel disease, 67.1% had previous myocardial infarction, and 89% had previous coronary interventions. The treatment groups were comparable at baseline. A mean of 19.7 laser/sham positions were obtained, and a mean of 78.7 pulses/sham were fired. The procedure was successfully completed in 97.5% of the laser group versus 97.6% of sham. Hospital mortality was 1.2%, one patient had a pericardiocentesis and there was one transient ischemic attack. Total mortality at 12 months was 7.3%. At 12 months 64% of patients in the laser group had improved 1 CCS class or more compared to 40% in the sham group (p=0.009). Improvement of 2 CCS classes or more was 36% versus 15% respectively (p=0.009). There was no significant increase in exercise time or oxygen uptake. We conclude that there is a significant improvement of angina symptoms after percutaneous myocardial laser compared to sham procedure.

P1805 Women with acute myocardial infarction or acute coronary syndromes benefit from an aggressive coronary intervention

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A high mortality risk for women with acute myocardial infarction (AMI) or acute coronary syndromes (ACS) after percutaneous coronary intervention (PCI) is a common finding in literature.

Study objective: to assess the impact of PCI on the outcome of a consecutive series of women with AMI or ACS treated with an aggressive invasive or medical strategy.

Population and methods: from Jan 1996 to Dec 2001, 983 consecutive women of 73±11 years of age were admitted to CCU for AMI (n=456) or ACS (n=527). PCI was performed in 581 patients (240 AMI and 341 ACS). Case load in our institution is about 120 PCI/year/operator.

Results: sixty-five patients died during hospitalization (6.6%). We analyzed the relationship between mortality and the following independent variables a) clinical presentation b) PCI therapy c) age (Table).

	AMI vs ACS	PCI vs no PCI	Age
ODDS RATIO	1.913	0.344	1.023
- 95% CL	1.106	0.189	0.997
+ 95% CL	3.310	0.625	1.050

Conclusion: women treated with PCI had a significant lower in-hospital mortality than women treated with an aggressive medical therapy. The benefit obtained with PCI was not influenced by the age of patients. Mortality was higher in patients with AMI.

P1806 Availability of on-site interventional facilities and clinical outcomes in patients acute coronary syndromes. Results from an Italian registry

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Aims: to compare management and clinical outcomes in hospitals stratified by the availability of on-site interventional facilities in a registry of consecutive patients admitted to italian hospitals for an acute coronary syndrome. Methods and Results: we studied 1074 patients enrolled in 25 hospitals in the Emilia-Romagna area over a 2-month period (Jan-March 2000). Only initial admissions were counted. Forty-nine percent of patients presented with ST elevation/BB (58% treated with a reperfusion strategy), 27% with ST depression, and 24% with T-wave inversion or a normal ECG. Thirteen percent of hospitals had 24-h, 30% day-only, and 57% no on-site interventional facilities. Six-month rates of coronary angiography (64%, 63%, 50%) and revascularization (46%, 47%, 33%) were higher in hospitals with increasing access to on-site facilities (P=0.0001). The presence of a 24-h on-site facility was the strongest predictor of angiography during the index admission (odds ratio 2.2, 95% CI 1.4-3.5). Only 15.3% of coronary angiographies were performed within 72 h from admission; 9% of patients received GPIIB/IIIA blockers. There were no major differences in patient outcomes during the index admission when hospitals were stratified by availability of on-site catheterization (in-hospital mortality 7.0%, 5.0%, and 7.0% respectively P=NS). Adjusted 6-month mortality was similar between groups of hospitals (odds ratio for hospitals with 24-h facilities 1.26 [0.76–2.08] and odds ratio for day-only 0.65 [0.35–1.18] compared to no availability). Conclusions: there is a significant variation in procedure use by the availability of on-site interventional facilities with no major differences in patient outcomes. Few patients however are aggressively treated with optimal anti-thrombotic therapy and early revascularization according to current clinical guidelines.

P1807 Acute myocardial infarction: is immediate surgical revascularisation justified?

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Background: Hemodynamic compromise and crescendo-angina require acute surgical intervention when PTCA measures alone are not successful. We stratified the risks of acute revascularisation with and without MI in contrast to urgent and elective bypass surgery.

Methods: 517 patients were investigated. 39 patients underwent acute revascularisation because of enzyme or ECG proven MI accompanied by crescendo-angina, hemodynamic compromise, or both. Necessity of intraaortic balloon pumping (IABP), temporary hemofiltration (CVVH), early mortality (EM), Cleveland-Score (CS), and EuroSCORE (ES) were compared with 32 emergent, 61 urgent, and 385 elective patients without MI, who underwent isolated coronary revascularisation. Multivariate risk factor analysis was performed.

Results: EM of the MI cohort was 15.4%, while 15.6% of the emergent, none of the urgent, and 2.1% of the elective patients deceased early. IABP was necessary in 49% MI patients, while performed in 28% emergent, 6.6% urgent, and in 2.6% elective cases. CVVH was performed in 29% of the MI, 15% of the emergent, 4.9% of the urgent, and in 3.4% of the elective patients. Preoperative risk factors, such as stability (stable, unstable, resuscitation), sex, body mass index, diabetes mellitus, and renal insufficiency did not influence EM but necessity of IABP and CVVH. CS was significantly higher in the MI group (8.5) than in the emergent cohort (5.8) while ES did not diclose differences between MI (9.6) and emergent patients (8.2). Both scores exhibited significantly higher values in the two immediate groups when compared to urgent (CS: 2.2; ES: 5.3) and elective (CS: 2.0; ES: 4.6) cases.

Conclusions: Patients undergoing immediate revascularisation had an elevated risk to die early independent from the presence or absence of acute MI. In almost two third of the patients with acute MI temporary CVVH was necessary implying a severely reduced perioperative hemodynamic condition. Although it should be addressed as a separated high risk group immediate revascularisation in the presence of acute MI is not contraindicated.

P1808 Rescue percutaneous thrombectomy catheter is less beneficial in acute myocardial infarction with large vessel diameter

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Background: Rescue Percutaneous Thrombectomy (PT) catheter is a new simple thrombectomy system to retrieve thrombi from the culprit lesion. The aim of this study was to identify clinical and anatomical characteristics, which may not benefit from Rescue PT catheter in patients with acute myocardial infarction (AMI).
Methods: Forty-nine consecutive inferior AMI patients, who had extensive thrombi in the diseased lesion and underwent primary coronary angioplasty, were enrolled in this study. TIMI frame count (TFC) was measured immediately after using Rescue PT catheter. We defined "inadequate reflow" as TFC>40 according to the previous report. The patients were divided into two groups: TFC =40 or less group (n=36) and TFC>40 group (n=13). Univariate and multivariate analysis were performed to identify clinical and anatomical factors in predicting "inadequate reflow" immediately after using Rescue PT catheter.
Results: There were significant differences between the two groups with regard to smoking, early reperfusion, bend lesion, and vessel diameter. In a multivariate model, large vessel diameter was the only independent predictor for "inadequate reflow" ($p<0.05$).

	TFC≤40 (n=36)	TFC>40 (n=13)	P value
Smoking	15 (42%)	10 (77%)	0.03
Reperfusion time (≤2h)	14 (39%)	0	0.01
Bend lesion (>45°)	16 (44%)	10 (77%)	0.04
Vessel diamter (mm)	3.0±0.5	4.0±0.4	<0.01

Conclusion: Large vessel diameter is independently associated with "inadequate reflow" immediately after using Rescue PT catheter in patients with inferior AMI.Patients Characteristics

CARDIOVASCULAR DISEASES IN THE 21ST CENTURY: THE CHALLENGES FOR NURSES

P1809 Why patients with myocardial infarction don't choose ambulance

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Background: The Swedish guidelines state that ST-elevation myocardial infarction (STEMI) patients should be admitted to hospital < 45 minutes and thrombolysis be given < 90 minutes after start of symptoms. Most ambulances have ECG-possibilities and telecommunication with the hospital. It's thus possible to start early prehospital treatment. The patients must therefore be aware of the advantages of the medical care that paramedics can offer. Earlier studies have shown that only 30% of patients with chest pain arrive at the emergency ward in ambulance. The aim of this study was to explain why the majority of patients with acute MI do not call emergency number 112.
Methods: 110 CCU-patients hospitalized because of acute MI filled in a survey regarding their thoughts and acts before the present hospital admittance.
Results: The patients stated in average 3 symptoms in connection with falling ill, where the most common symptom was chest pain. The dominating character was "oppression" (42%). They experienced their symptoms as "anxieting" (41%), "discomforting" (36%) and "troublesome" (31%). 39% delayed >2 hours before seeking medical care. Anyhow 38% decided to seek already < 30 minutes. Altogether 77% considered their symptoms to be related to the heart. Of the rest, 65% delayed >1 hour. 62% arrived by ambulance directly to the hospital, but only 6 patients called themselves. Mostly the spouse (40%) contacted the alarm centre. Those with symptoms for a shorter time, and being at home chose the ambulance more frequently than those who fell ill somewhere else and had symptoms for a longer time. The most common reason for not choosing ambulance was the feeling that " I am not sick enough " (43%), "I never thought about it" (38%) or "Unnecessary to order ambulance" (26%). In a multiple regression analysis the reasons for not choosing ambulance turned out to be: daily work, tiring symptoms and "this is probably not serious and will pass". Predictor for choosing ambulance was nausea/coldsweat, unbearable or cramping pain and high pain-intensity. STEMI-patients choosing ambulance, reduced their delay-time to reperfusion by 21 minutes.
Conclusion: The ambulance is not an option for patients unless they feel really sick. The time gain is anyhow of great importance for those STEMI-patients choosing the ambulance.

P1810 Morbidity and mortality in patients with myocardial infarction complicated by nosocomial infection

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Introduction: Complications of myocardial infarction (MI) are responsible for a significant percentage of deaths. Information regarding the importance of nosocomial infection as a complication of MI is lacking. This study analyzed the incidence and the impact of infectious complications of MI on morbidity and mortality as well as its relation with the invasive procedures undergone in this setting.
Methods: This was a retrospective and clinical study, performed by the analysis of medical records. The population of the study was constituted by patients admitted with a confirmed diagnosis of MI, from January 1996 to December 1999, at the Coronary Care Unit from the Heart Institute of the University of Sao Paulo Medical School in Brazil.
Results: 1,227 patients were analyzed, 60 (4.89%) of them fulfilled the diagnostic criteria of a nosocomial infection complicating MI (Infected Group). The other 1,167 patients constituted the Control Group. Univariated analysis indicated that the mean age (67.5 and 62.6 years old, p=0.003), the length of hospital stay (26.6 and 12.0 days, p=0.0000) and mortality (45% and 12.25%, p=0.0000) were greater in the Infected Group than in the Control Group respectively. Predictors of mortality assessed by multivariate analysis were age and being part of the Infected Group. Every 10 years increment on age was associated with an odds ratio for mortality of 1.31 for the Infected Group and 2.15 for the Control Group. For a patient with 60 years old, the odds ratio for mortality is 40.01 if in the Infected Group and 7.71 if in the Control Group. In the Infected Group, the average of invasive procedures done per patient was 3.38 and correlated to Killip class and mortality. The most frequent infections were pulmonary (63.3%), urinary tract (36.6%) and blood (8.3%).
Conclusion: Nosocomial infection, as a complication of myocardial infarction has a great impact on morbidity and mortality in patients admitted in the coronary care unit.

P1811 Status of CPR in the Swedish population in the year 2000. A nation wide survey

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Aim of this study was to determine the proportion of cardiopulmonary resuscitation (CPR) trained adults in Sweden and the non-trained population's willingness to be trained in CPR.
Methods: In a nation wide survey 5000 randomly selected adult inhabitants, aged 18 to 79 years, were approached with a postal questionnaire, resulting in 3159 responders. Sweden has 6.5 million inhabitants in the current ages, the sample was randomly selected by the Swedish person and address register and stratified to correlate to the population's geographically distribution. The questionnaire was constructed by the investigators and based on previous questionnaires used by the research-group.
Results: The mean age was 46 (± 16) years and 54% of the respondents were women. 11% respondents were born outside Sweden and 9% could be regarded as professionals (health and rescue personnel). 45% (n=1417) had been trained in CPR and nearly half had been trained more than once and 52% reported having trained CPR 1996 or more recently. The most common reasons given for CPR education was job requirement and general interest. Among the non-trained responders 50% was willing to learn CPR (both chest compression and mouth-to-mouth ventilation). Of the 847 respondents reporting unwilling or unsure to learn CPR 12% were willing to learn CPR if only chest compressions were included. Regarding the reason not to be trained, it was most common not to know about the possibility to have a CPR course (26%) and 14% did not know where or how to receive CPR training. 21% stated that they had not had the interest of learning CPR. 416 respondents (13%) reported having witnessed a cardiac arrest and 4% (120) reported having performed CPR without professional obligations.
Conclusion: From this survey it can be assumed that about 45% of the adult Swedish population is trained in CPR and 4% have used their knowledge in a situation of cardiac arrest. Half of the non-trained population is willing to learn CPR but it is common not to know about the possibilities to receive CPR training. The Swedish population is highly willing to learn CPR but the community and the educating organisations should intensify their information about the possibilities to receive CPR training.

P1812 Anxiety and well-being in first-time coronary angioplasty patients and repeaters

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Introduction: Preparatory information before an invasive procedure has been shown to have positive effects (e,g, on recovery, anxiety and well-being). However, preparation of patients for a repeat procedure is hardly investigated. The question is whether these patients benefit from the same preparatory information. Aims: To determine whether there are differences in terms of anxiety and well-being between patients undergoing their first Percutaneous Transluminal Coronary Angioplasty (PTCA) and those undergoing a repeat PTCA, and secondly to gain information on how patients prepare themselves for a repeat PTCA. Design: Descriptive correlational study with a quantitative and qualitative research component. Method: First-time PTCA patients (n=46) and re-PTCA patients (n=40) were asked to complete three psychological self-report questionnaires (HADS, HPPQ and VAS) the evening before the procedure. Five re-PTCA patients were interviewed the day after the procedure. Results: The anxiety scores (HADS and VAS) show a trend towards a worse condition in the re-PTCA group: HADS 6.5 versus 5.0 and VAS 4.0 versus 2.6. The HPPQ reveals a slightly lower well-being in re-PTCA patients: 18.0 versus 19.0. These differences between the two groups are not statistically significant. Once the interview data were coded, four themes were apparent, namely: recurrent symptoms, information, experience and future prospects. Conclusion: A trend is seen towards a worse condition in the re-PTCA group with respect to anxiety and well-being. However the observed differences are not significant, they seem to be clinically relevant. The interviews point out that the return of symptoms and future prospects, rather than the procedure itself, are an important part in preparing for a repeat intervention. This aspect is currently no part of the provided preparatory information. Future research will have to determine the most beneficial method of preparing these patients (e.g. tailored preparation, emotional support, coaching).

P1813 Early discharge after coronary angiograms using the femoral approach

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Femoral approach is stablished as a safe one for coronary angiograms; however, the consecutive bed-rest increases hospital stay and costs.
Objective: To report the incidence of events in patients submitted for coronary angiograms (CA), using femoral approach (FA) with early hospital disharge (EHD) 3 hours after the procedure.
Material and Methods: We analyzed 300 consecutive patients (51.5 years, 86% male and 87,5 kg mean weight) submitted for CA, using FA (6 french introducers), heparin dose 1000 UI and EHD, in the period 01/2001 to 01/2002.
Exclusion criteria: Age >75 years, coronary angioplasty, manual compression>15 minutes to achieve an effective groin hemostasis and refusal of this technique by the refering physician. After 3 hours bed-rest, all pts. were discharged one hour after a professional-asisted walk. We report the following clinical events: 1- Ischemic: angor or death; 2- Hemorrhage: minor and major using TIMI criteria.
Results: No patients presented ischemic events or major hemorrhage. 98,66% (n=296) of this population have an uncomplicated walk after 3 hours bed-rest and hospital discharge one hour later. One patient was excluded from analysis due to severe hypotension. Only 3 patients (1%) suffered one minor hemorrhagic event, all well managed with additional local compression. No seudoaneurisms were reported.
Conclusion: Early discharge after coronary angiograms using the femoral approach emerged as an effective and safe strategy, reducing hospital stay and costs.

P1814 Ambulatory blood pressure monitoring: nurse management

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Background: Ambulatory blood pressure monitoring (ABPM) is relatively easy to use, and yields many more BP parameters than do clinic BP measurements. However, it might be inaccurate for a variety of reasons: incorrect technique, operator error, and environmental factors. The patient's compliance may significantly limit the feasibility of ABPM. A nurse assistant can easily be trained to follow a standardized procedure. The aim of the study was to evaluate the efficacy of a nurse management of ABPM.
Methods: We studied 466 patients (358 male; 56±11 years) submitted to ABPM in the last two years. We have experienced a nurse management of ABPM in the last 12 months (N = 253 pts). All nurses had been previously undergone to a specific training, which allowed the practice of both the instrument and the software. A standard protocol was then performed in order to obtain in each patient the accurate identification of clinical history, risk factors (such as age, gender, family history, diabetes, smoke, dislipidemia and hypertension) and related diseases (such as coronary artery disease, cerebro-vascular disease and peripheral arterial disease). To obtain the highest patient compliance and to reduce the incidence of incomplete measurements, each patient was adequately informed about the exam characteristics.
Results: A significant reduction of the mechanical problems of the instruments was obtained, as compared with the previous year (2% vs 19%; $p<0.05$). Moreover, also the number of not diagnostic exams (correct measurements <85%), due to technical problems or lack of patient compliance, was significantly reduced (7% vs 25%; $p<0,05$). All the obtained data were stored in a database, thus available for medical epidemiological and statistical analysis.
Conclusions: The management of ABPM by trained nurses seems to improve the quality of the test, to increase the patient compliance and to collect all the data available to further statistic analysis.

P1815 SCAN: Smoking Cessation by Ambulant Nurse-intervention

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SCAN: Smoking Cessation by Ambulant Nurse-intervention
A randomised study of the effect of a smoking cessation programme in patients admitted to a coronary care unit with a 12 months' follow-up.
Smoking is still the most significant cause of ischemic heart disease. In Denmark approximately one third of the adult population can be classified as smokers. The purpose of this study was to evaluate the effect of a systematic intervention programme. The smoking cessation programme followed the nationally approved guidelines.
Material and methods: SCAN is a randomised,prospective intervention study of the effect of a systematic smoking cessation programme. The entire programme was conducted by specially trained nurses.
During a period of two years all patients admitted to the coronary care unit were screened.
Smokers motivated for participation in the study were randomised into either intervention group (I) or control group (C). All patients in the I-group were offered five individual consultations with a nurse specially trained to give information about smoking cessation.
All patients in the I and C group received the usual standard information at the department about cardiac risk factors and possible prophylactic precautions.
All participants were contacted by telephone 3, 6 and 12 months following discharge. None of the nurses from the intervention programme were involved with this part of the study.
Results: Among the 3.982 screened patients 1.175 (29,5%) were smokers. Out of those 105 (9%) fulfilled the inclusion criteria and were randomised into either group I or C respectively. Smoking cessation after 12 months in the two groups were as follows: 63% in group I and 50% in group C respectively. This result showed a insignificant difference between the two groups.
Conclusions: The proportion of smokers in the screened population was lower than expected.
Only one out ten smokers was motivated for participation in the study.
The lack of effect of the intervention programme could be explained by the fact that all patients randomised were highly motivated which can be supported by the relatively high numbers of non-smokers in both groups after 12 months.
It is our recommendation that future studies should focus on the prognosis of the 91% of smokers who were unwilling to participate in a systematic intervention programme.

P1816 Are cardiac rehabilitation programmes needed in hospital practice?

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Background - Cardiac rehabilitation has shown to be beneficial and is stimulated through international guidelines. Programmes that define the delivery of cardiac rehabilitation are available for outpatient care, but not for the hospital phase.
Aim - To assess the need for inpatient cardiac rehabilitation programmes, we investigated the extent to which cardiac rehabilitation guidelines are followed during hospital care.
Methods - We included 83 consecutive patients hospitalised for myocardial infarction, angina or first diagnosis of heart failure. To assess whether topics in the guidelines on cardiac rehabilitation (secondary prevention, physical exercise, handling chest pain, and psychosocial support) were addressed during hospitalisation, activities related to cardiac rehabilitation were abstracted from medical and nursing charts, after hospital discharge. To assess a patients's need for cardiac rehabilitation (i.e., presence of cardiovascular risk factors or anxiety as measured with the Hospital Anxiety Depression Scale) patients were asked to fill out a questionnaire on the 5th day of hospitalisation.
Results - Of the 64 patients (77%) who had cardiovascular risk factors, 52% of them were provided with information, advice or the offer to start with a guided programme. For example, support was registered in 58% of 45 smokers, 43% of 28 patients with a high cholesterol level (>= 5 mmol/L), 2% of 47 patients who are overweight (BMI >= 25 kg/m^2), and 2% of 48 patients with a sedentary lifestyle. In 99% of all patients, information, advice or guidance regarding exercise tolerance was documented. For instance, in 88% the presence or absence of chest pain was registered, and progress in mobilisation was considered in 51% of all patients. With regard to handling chest pain, 16 patients (19%) reported that they would not take nitro-glycerine in case of chest pain. The psychosocial situation was documented in 54% of all patients. However, none of the 19 patients (20%) who experienced anxiety received the attention needed.
Conclusion - Currently, cardiac rehabilitation during hospitalisation is mainly focussed on physical recovery. Insufficient attention is given to patients' psychosocial situation, handling chest pain, and cardiovascular risk factors. Our results show which areas of in-hospital cardiac rehabilitation require additional attention. We recommend the development of multidisciplinary inpatient cardiac rehabilitation programmes to meet the needs of in-hospital patients.

P1817 Impact of an educational program through a new nurse heart failure knowledge score

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Background: Multidisciplinary heart failure disease management improve clinical outcomes in congestive heart failure patients. Evaluation and validation of educational intervention remain a controversial and difficult process. Establishment of a "knowledge score" could provide some insight about patients need and help practitioners in prescribing educational intervention. The aim of this pilot study was to evaluate a new score of knowledge in heart failure patients before and after education session.
Method: In this study, 21 patients (mean age: 56±18 years, 71.4% of male, 29.4% of left ventricular ejection) attended an education session of one day about heart failure. A multidisciplinary program was established in collaboration with physician, nurse, dietician, physiotherapist and medical social worker. Using a self-questioning data sheet prepared in collaboration with nurses leading the educational program, we analysed six major topics: knowledge about disease, clinical evaluation (signs and symptoms of deterioration of heart failure), daily physical activity, diet, medical follow-up and medical treatment. Multiple choice questions were used to evaluate level of knowledge for each topics. Each answer was rated with points to obtain an end score from 0 to 20 for each topic. Evaluation was made before and one month after heart failure education session.
Results: Evolution of the knowledge score after the education program is presented for each topic as follow (before vs after): knowledge of disease (9.45 vs 18.33), clinical evaluation (7.12 vs 13.50), physical activity (6.74 vs 11.60), diet (7.57 vs 14.36), medical follow-up (12.19 vs 17.95) and medical treatment (7.98 vs 14.43). All these results were statistically significant ($p<0.0001$).
Conclusion: This pilot study confirms that i) our knowledge score is feasible, ii) the level of knowledge about heart failure in patients of South West of France is low, iii) heart failure education program improves significantly knowledge of our patient as assessed by this score. A validation of this knowledge score remains necessary with larger study.

P1818 Individual quality of life assessment in adults with congenital heart disease

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Many patients with congenital heart disease experience the heart defect intruding on their daily life. The aim of this study was to examine quality of life (QOL) and its individual determinants in adults with congenital heart disease.
Methods: This cross-sectional study included 134 patients (67.2% males). QOL and its determinants was measured using a Visual Analogue Scale (VAS) ranging from 0 to 100, and the SEIQoL-DW, respectively. This latter instrument comprises 3 successive steps: (1) nomination by the respondent of the 5 areas most important for his/her QOL, (2) rating of the actual status for each specified area on a VAS from 0 to 100, and (3) quantification of the relative importance of each nominated area in comparison with each other, using a 5-segment disk.
Results: Patients perceive their overall QOL as good (VAS median 80; Q1=73; Q3=86). The SEIQoL-DW identified 13 areas affecting patients' QOL. The table describes the percentage of patients reporting the respective areas (step 1), the median actual status (step 2), and the relative importance for each cue (step 3).

individual quality of life measured usin

	Step 1	Step 2	Step 3
Significant others	73.9%	85.5	23%
Job/education	51.5%	68	18%
Leisure	50%	74	17%
Health	49.3%	76	23%
Social network	49.3%	75	20%
Personal values with respect to others, life and society	47%	79	20%
Financial means and material well-being	29.9%	67	16%
Psychological well-being	14.2%	76	19%
Capacities and impediments due to the heart defect	11.9%	49	17%
Future	10.4%	80	20%
Health care	3%	87.5	16.5%
Nourishment	3%	76	12%
Pets	2.2%	91	27%

Conclusion: Individual QOL assessment in adults with congenital heart disease provides a detailed picture of issues relevant for QOL. These issues should be addressed in comprehensive health care, aiming at improving patients' QOL.

MYOCARDITIS AND PERICARDITIS

P1819 Celiac disease associated with autoimmune myocarditis

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Background: Both celiac disease (CD) and myocarditis can be associated with systemic autoimmune disorders; however the coexistence of the two entities has never been investigated while its identification may have clinical impact.
Methods: We screened the serum of 187 consecutive patients (pts) with myocarditis (118 M, 69 F, mean age 41.7±14.3 years) for the presence of cardiac autoantibodies, anti-transglutaminase (IgA-tTG) and anti-endomysial antibodies (AEA). IgA-tTG and AEA positive pts underwent duodenal endoscopy and biopsy and HLA analysis.
Results: Thirteen of the 187 pts were positive for IgA-tTG and 9 of them (4.4%) for AEA. These 9 pts had iron-deficient anemia and duodenal endoscopic and histologic evidence of CD. CD was observed in 1/306 (0.3%) of normal controls ($p<0.003$). In CD pts myocarditis manifested with heart failure in 5 pts and ventricular arrhythmias (Lown class III-IVa) in 4. At histology a lymphocytic infiltrate was present in 8 pts and giant-cell myocarditis in one; circulating cardiac autoantibodies were positive and myocardial viral genomes negative in all. HLA of pts with CD and myocarditis was DQ2-DR3 in 8 pts and DQ2-DR5(11)/DR7 in one. The 5 pts with myocarditis and heart failure received immunosuppression (azathioprine 1 mg/Kg/daily for 5 months and prednisone 1.25 mg/Kg/daily for 4 weeks tapered to 0.33 mg/Kg/daily for 5 months) and gluten-free diet with recovery of cardiac volumes and function. The four pts with arrhythmias, put on gluten-free diet alone, showed arrhythmias' improvement (Lown Class I).
Conclusions: A common autoimmune process toward antigenic components of myocardium and small bowel can be found in >4% of pts with myocarditis. In these pts immunosuppression and gluten-free diet can be effective therapeutic options.

P1820 Immunomodulation of murine Coxsackie B3 myocarditis with interleukin-15

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Cytokines play an important role both for the initiation and perpetuation of viral myocarditis. We examined the influence of IL-15, an important proinflammatory cytokine, on the course of myocarditis in the Coxsackie B3 (CB3) infected mouse.

Methods: Eight-week-old male BALB/c mice were intraperitoneally infected with 500000 plaque forming units of CB3, strain Nancy, and subsequently treated with daily injections of recombinant murine IL-15 (330ng) or an equivalent dose of IL-15 fusion protein (250μg), which inhibits the physiological effects of IL-15. After twelve days the slope of the left ventricular pressure pulse was measured with a Millar-tip catheter in the anesthetized and respirated animal. Uninfected and infected animals without further treatment served as controls. For immunohistological evaluation cryosections of the hearts were prepared and stained with monoclonal antibodies against several leukocyte surface antigens.

Results: Infected and uninfected respectively infected and IL-15 treated animals showed significant differences in regard to body weight, left ventricular function and cellular infiltrates in the myocardium (see table). Treatment of infected animals with IL-15 resulted in an almost normal body weight, whereas animals that were infected and injected with IL-15 fusion protein showed the lowest body weigths. Similar results were seen for the slope of the left ventricular pressure pulse as a parameter for the left ventricular function.

	Uninfected (n=14)	Infected (n=14)	Infected + IL-15 (n=6)	Infected + IL-15 fusion protein (n=6)
body weight (g)	26.8 ± 2.5	20.11 ± 2.3	24.5 ± 3.3*	19.4 ± 0.8**
dP/dt max (mmHg)	5928.7 ± 1206.1	4377.8 ± 953.8	5862.2 ± 1174.9*	3871.5 ± 471.9**
CD4-positive cells (cells/hpf)	0.006 ± 0.015	0.877 ± 0.3	0.544 ± 0.16*	0.619 ± 0.33**

*p<0.05 compared to infected, **p<0.05 compared to uninfected

Conclusions: Treatment with IL-15 showed a positive effect on the clinical course of CB3 induced murine myocarditis, whereas inhibition of the intrinsic IL-15 with fusion protein had a detrimental effect.

P1821 Beneficial effects of interleukin-4 on the regulation of cardiac function, MMP-3 and TIMP-1 expression in murine myocarditis by the induction of TGF-β1

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Cytokines are involved in the regulation of myocardial extracellular matrix remodelling. Aim of this study was to analyze the in vivo roles of IL-4 for the mRNA expressions of myocardial metalloproteinase-3 (MMP-3), tissue inhibitors of MMPs (TIMP-1) and TGF-β1 during coxsackievirus B3 (CVB3; Nancy strain; 500000 PFU)-induced myocarditis in BALB/c mice. Myocardial samples from infected (n=8) and uninfected control (n=8) BALB/c mice under the treatment of murine rIL-4 (200 ng/mouse/day; i.p.) as well as infected (n=8) and uninfected control (n=8) mice without treatment at ten days after coxsackievirus B3 inoculation were analyzed by semi-quantitative RT-PCR. In viral infected mice, left ventricular dysfunction, upregulated MMP-3 and downregulated TIMP-1 were demonstrated. IL-4 treatment led to significant improvement of left ventricular function, suppression of MMP-3 mRNA induction as well as the increment of TIMP-1 mRNA. In addition, the effects of IL-4 treatment was associated with an significant induction of TGF-β1 expression (Table).

	MMP-3	TIMP-1	TGF-β1
control (n=8)	0,66±0,24	1,33±0,29	0,74±0,11
infected (n=8)	1,21±0,22*	0,34±0,11*	1,18±0,13*
infected+IL-4 (n=8)	0,85±0,05**	0,89±0,07**	1,64±0,04**

*p<0,05 vs control; **p<0,01 vs infected.

Conclusions: The suppression of MMP-3 induction and the increment of TIMP-1 expression may contribute to the improvement of left ventricular function through the upregulation of TGF-β1 by IL-4 mediated immunomodulation.

P1822 Beneficial effects of gene-transfered interleukin-10 on autoimmune myocarditis in the rat

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Effectiveness of the immunosupressive therapy of myocarditis is controversial, although it has attracted a great deal of attention. Interleukin (IL)-10 has a variety of immunomodulatory properties. We examined effects of murine IL-10 (mIL-10) gene transfer on the heart failure induced by experimental autoimmune myocarditis in the rat. Nine-week-old Lewis rats were immunized with pig cardiac myosin (day 0). These immunized rats developed myocarditis during day 14 to 21 with sever inflammatory changes. The morbidity of this experimental autoimmune myocarditis was 100% in the rats. A plasmid vector expressing mIL-10 cDNA (800 μg/rat) was transferred into the tibialis anterior muscles by electroporation and control rats received empty plasmid. Because of the limitation of its expression duration, we used three times applications of electroporation (5 days before immunization, day 4, and day 13 after immunization). The 21-day survival in rats treated with mIL-10 cDNA was higher (20/20 = 100%) than that in the control group (18/24 = 75%). Furthermore, mIL-10 treatment significantly attenuated myocardial lesions and improved hemodynamic parameters on day 21. The 49-day survival in mIL-10-treated rats was higher (10/10=100%) than that in the control group (8/10=80%). Hemodynamic parameters were also improved by mIL-10 treatment. These findings showed that gene transfer into muscle by electroporation in vivo is an effective means of delivery of IL-10 for the treatment of heart failure induced by autoimmune myocarditis and IL-10 does not delay the onset of autoimmune myocarditis but suppresses it.

P1823 Cardiac magnetic resonance imaging for diagnosis of viral myocarditis – significance of MRI-guided endomyocardial biopsy

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Purpose: Definite diagnosis of myocarditis is only possible by histological and molecularpathological analysis of endomyocardial biopsies. As reported an estimated number of 17 biopsy specimens are required to achieve a sensitivity of 80% for diagnostic of myocarditis if unguided biopsy sampling is performed. In this study, inflammatory myocardium was prospectively visualized by MRI. To minimize the sampling error, target-specific biopsies were taken from left ventricular areas as detected by MRI.

Methods: In 42 patients with suspected myocarditis, ECG-triggered cardiac MRI studies were performed using a 1,5 T scanner. T2-weighted images included a single-shot "HASTE"-sequence and a fat-suppressed "inversion recovery"-sequence. T1-weighted images were performed in breath-holding technique, unenhanced, and after gadolinium injection. The MRI was considered positive if myocardium with increased signal intensity was detected in T2-weighted images with and without fat-suppression. In each patient 4 left ventricular biopsies were taken from the suspected area. Biopsies were considered positive in case of acute myocarditis (with myocyte necrosis), in case of chronic myocarditis (with an increased number of T-lymphocytes and/or macrophages with or without viral genome) or in case of virus persistence without cellular inflammatory reaction. Viral genome in myocardial biopsies were detected by PCR and in situ-hybridisation. Biopsies without an increase of inflammatory cells and without viral genome were considered negative.

Results: Acute myocarditis with evidence of viral genome was detected once; chronic myocarditis was diagnosed in 14 patients (33%), with evidence of viral genome in 11 cases. Virus persistence was observed in 10 patients (24%). Biopsies were negative in 17 patients (41%). MRI studies were positive in 14 of 15 patients (93%) with acute or chronic myocarditis proven by endomyocardial biopsy. MRI study was negative in 11 of 17 patients with negative biopsy. MRI revealed a sensitivity of 93% and a specifity of 52% to prove myocarditis resulting in a negative predictive value of 93% and a positive predictive value of 52%.

Conclusion: Cardiac MRI serves as a noninvasive screening method in suspected myocarditis. MRI facilitates myocardial biopsy of topographically defined foci. The MRI-guided endomyocardial biopsy reduces the otherwise inevitable sampling error and minimizes effectively the number of biopsy specimens needed to get the definite diagnosis of myocarditis with high sensitivity.

P1824 Lone HCV myocarditis responsive to immunosuppressive therapy

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Objectives: This study analyses the causal role of HCV infection in patients with lone myocarditis and its susceptibility to an immunosuppressive therapy.
Methods and Results: Among 49 consecutive patients with myocarditis serologically screened for HCV in addition to other cardiotropic viruses, four had anti-HCV antibodies. Clinical manifestation was severe heart failure in three cases and chest pain with left bundle branch block (LBBB) and moderate cardiac dysfunction in one case. These 4 patients underwent 2D-echo, coronary angiography and endomyocardial biopsy. Nested-polymerase chain reaction (PCR) for positive and negative strand of HCV was performed on sera and myocardial samples. PCR was also used to detect genomic sequences of cardiotropic viruses including enterovirus, adenovirus, influenza virus A and B, herpes simplex viruses, Epstein Barr virus, parvovirus B19 and cytomegalovirus. HCV in the myocardium was detected by TORDJI-22 antibody. Five subjects without myocarditis, two with and three without HCV infection, were used as controls. Histologically, a lymphocytic myocarditis associated with myocytes positively stained by TORDJI-22 was shown in all. Cardiac autoantibodies were detected in all cases. Nested-PCR showed both positive and negative strands of HCV RNA in serum and myocardium, while other viral genomes were absent. None of the five controls had HCV RNA in the myocardium. Patients were treated with prednisone and azathioprine for 6 months. Recovery of cardiac volumes and function occurred in all patients with disappearance of chest pain and LBBB in patient 4. At 4-weeks control biopsy myocarditis progressed to a healed phase, though HCV RNA was still detectable in the serum and myocardium. Cardiac improvement was maintained at 12 month overall follow-up.
Conclusions: HCV can be detected in the myocardium of as many as 8% of patients with lone myocarditis; HCV myocarditis can benefit from immunosuppression despite persistence of viral genome, suggesting an immunomediated mechanism of damage.

P1825 Prevalence of parvovirus B19 genome in endomyocardial biopsies

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Introduction: Although enteroviruses were considered the most common cause of inflammatory heart muscle diseases, Parvovirus B 19 (PB 19) has become a new and frequent candidate for myocarditis (M) and dilated cardiomyopathy with (DCMi) and without inflammation (DCM). Infection with PB 19 can lead to several clinical manifestations, which include myopericarditis, erythema infectiosum, arthropathy, hydrops fetalis as well as acute hepatitis. PB 19 genome has been shown in the myocardium and liver tissue.
Methods: We investigated leftventricular endomyocardial biopsies (EMB) from 110 consecutive patients with clinically suspected inflammatory heart disease for the presence of parvovirus B19 genome by polymerase chain reaction (PCR). Diagnosis of M, DCM, DCMi and perimyocarditis (Pm) was confirmed by clinical data as well as immunohistochemical and histopathological investigations of the EMB. A control group consisting of patients with arterial hypertension was investigated, too. Results: The prevalence of PB 19 genome was highest in patients with DCMi (23%) and patients with myocarditis (19%); in patients with DCM and Pm the prevalence was 16%. In patients with resolved M no PB 19 genome was detected, in patients with no inflammation and controls prevalence was 4% and 7%, only.
Conclusions: These findings suggest an association of parvovirus B19 genome in the EMB of adults with the development of DCM, DCMi and chronic myocarditis in far more cases than previously expected. PB 19 should be recognized as a potential cardiogenic pathogen in patients of all ages. An early treatment of persistent PB 19 infection by immunoglobulins should be worth striving to prevent cardiac complications and the development of left ventricular dilatation and heart failure.

P1826 Pericardial cytokines in pericarditis versus coronary artery disease

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Background: The activation of cytokines in various forms of pericarditis is incompletely investigated. To elucidate this issue we have analyzed IL-6, TGF-beta1, TNF-alpha, IFN-gama, and GM-CSF in pericardial effusion (PE) and serum of patients with pericarditis and in pericardial fluid of bypass surgery patients.
Methods: Pericardial fluid was obtained after pericardiocentesis (Group 1: 30 pericarditis patients, 60% males, 52.4±14.2 years) or after sternotomy (Group 2: 21 bypass surgery patients, 42.9% males, 67.2±7.4 years). Samples were promptly aliquoted, frozen and stored at -70°C. The cytokines were estimated using quantikine enzyme amplified-sensitivity immuno-assays (R&D Systems, MN). Cytokines concentrations in pericardial fluid of group 1 (40% neoplastic, 23.3% autoreactive, 13.3% viral, 13.3% lymphocytic, and 10% iatrogenic PE) were compared with serum levels, and with group 2.
Results: IL-6 was significantly increased in PE in comparison to serum in all forms of pericarditis and increased in comparison to pericardial fluid of by-pass surgery patients (except in autoreactive PE). TGF-beta1 was strikingly lower in PE than in serum of all pericarditis patients. However, TGF-beta1 PE levels were significantly higher in all patients in Group 1 than in Group 2, except in infectious pericarditis. TNF-alpha was increased only in PE of patients with infectious pericarditis in comparison to Group 2. IFN-gama levels did not significantly differ between PE and serum or in comparison to Group 2. GM-CSF was present only in small proportion of patients with neoplastic and autoreactive PE.
Conclusions: Significant differences in the activation of IL-6 and TGF-beta1 in pericardial effusion in comparison to serum values in the same patients and in the pericardial fluid of by-pass surgery patients implies their possible role in the pathophysiology of the disease. The pattern "high TNF-alpha/low TGF-beta1" was found in infectious pericarditis and low IL-6 in autoreactive pericardial effusion.

P1827 Chronic versus recurrent pericarditis: should we give colchicine to everybody?

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Background: Colchicine has been successfully applied in the management of patients with recurrent and acute pericarditis. The aim of the present study was to investigate its therapeutic effect in chronic non-recurring pericardial inflammation.
Methods: Study population included 17 patients with idiopathic pericardial effusion. Group 1 comprised seven patients with idiopathic chronic non-recurring pericarditis (28.6% males, mean age 50.4±18.2 years). Additional ten patients with idiopathic recurring pericarditis were assigned as Group 2 (30% males, mean age 52.7±5.1 years). All patients were resistant to previous non-steroid anti-inflammatory (NSAI) treatment. In both groups colchicine was given at a loading dose of 2 mg for one week and a maintenance dose of 1.5 mg daily for five months, tapering of the doses by 0.5 mg per week in additional three weeks. All patients were included in monthly clinical and echocardiography follow-up for the period of 12 months.
Results: During the six-months of treatment period colchicine was effective in relieving symptoms in 28.6% of pts from Group 1 vs. 80% of pts from Group 2 ($p<0.05$). Furthermore, colchicine regimen resulted in disappearance of the pericardial effusion in 14.3% of pts from Group 1 vs. 60% of pts from Group 2 ($p<0.05$). In additional six months follow-up after the withdrawal of colchicine treatment the therapeutic effect remained unchanged.
Conclusion: Efficacy of six-months colchicine regimen was very low in pts with chronic idiopathic non-recurrent pericarditis in comparison to patients with recurrent pericarditis, both regarding symptoms relief and disappearance of pericardial effusion. In patients with recurrent pericarditis therapeutic effect remained unchanged six months after the withdrawal of medications.

P1828 Feasibility and diagnostic value of pericardial biopsy: the role of flexible percutaneous pericardioscopy

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Background: The clinical significance of pericardial biopsy is controversial. The aim of the study was to assess the feasibility and diagnostic value of three approaches to pericardial biopsy: fluoroscopic control and standard sampling, pericardioscopy guidance with standard or extensive sampling.
Methods and Results: Forty-two subsequent patients with a large pericardial effusion underwent parietal pericardial biopsy. In group 1 (12 patients, 66.7% males, age 46.7±12.2 years) pericardial biopsy was guided by fluoroscopy (3-6 samples/patient). Group 2 included 22 patients (50% males, age 50.8±10.4 years) undergoing 4-6 pericardial biopsies/patient guided by pericardioscopy (16F flexible endoscope). In group 3 extensive pericardial sampling was performed guided by pericardioscopy (10 patients, 60% males, age 42.3±14.6 years, 18-20 samples/patient). Sampling efficiency was better with pericardioscopy (group 2 - 84.9%; group 3 - 87.3%) in comparison to fluoroscopic guidance (group 1 - 43.7%; $p<0.01$). Diagnostic value was defined as: a new diagnosis uncovered, etiology revealed, clinical diagnosis confirmed, and the biopsy false negative. Pericardial biopsy in group 3 had higher diagnostic value than in group 1 in revealing new diagnosis (40% vs. 8.3%, $p<0.05$) and etiology (50% vs. 8.3%, $p<0.05$). In group 2 pericardial biopsy had a higher yield in establishing etiology than in group 1 (40.9% vs. 8.3%; $p<0.05$). Pericardial biopsy was false negative in 58.3%, 45.4%, and 10% in groups 1, 2, and 3, respectively. There were no major complications.
Conclusions: Pericardioscopic guidance enhanced pericardial sampling efficiency. The diagnostic value of pericardial biopsy was significantly improved by extensive sampling made possible by flexible percutaneous pericardioscopy.

P1829 High prevalence of enterovirus infection in chronic, effusive pericarditis

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Background: Clinical and experimental studies suggest persistent enteroviral infection in chronic pericarditis, but direct evidence of viral infection in pericardial tissue has been lacking.
Materials and Methods: Formalin-fixed, paraffin-embedded pericardial samples from 4 patients with chronic effusive pericarditis and 7 patients with chronic constrictive pericarditis of unknown origin were obtained in Changzhou Hospital, Hebei Province, China and Zhongshan Hospital, Shanghai, China. These were investigated for enteroviral capsid protein VP1 by immunohistochemical staining with the enterovirus group-specific monoclonal antibody D8/1 and for virus genomic RNA by nested RT-PCR or in situ hybridization with group-specific oligonucleotides. Pericardial tissue collected during surgical resection from 3 patients with chronic tuberculous pericarditis was used for comparison. Myocardial tissue from a pediatric case of fatal, acute enteroviral myocarditis was used as positive control.
Results: Enteroviral capsid protein VP1 was found in pericardial tissue from 3 of 4 (75%) cases of effusive pericarditis and 1 of 7 cases (14.3%) of constrictive pericarditis. nRT-PCR and in situ hybridization showed enteroviral RNA in one case of effusive pericarditis only, which was positive also for viral capsid protein. The nucleotide sequence of RT-PCR-amplified enteroviral RNA, determined by automatic cycle sequencing in both orientations, was most homologous with poliovirus type 3. Capsid protein VP1 and viral genomic RNA were both present in autopsy tissue from the case of acute myocarditis but neither was found in tissue from any case of tuberculous pericarditis.
Conclusions: This is the first study to show the persistence of enterovirus antigen and viral RNA in pericardial tissue and indicates that enteroviruses are frequently involved in chronic, effusive pericarditis.

P1830 Regulation of eNOSs expression by aspirin in pericardial tissue during inflammation

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The aim was to analyze if pericardial tissue expresses endothelial nitric oxide synthase (eNOS) protein and to determine the presence of cytosolic proteins that bind to eNOS mRNA favouring its destabilization. The effect of aspirin on the above mentioned parameters was also analyzed. eNOS protein was expressed in pericardial tissue from male guinea-pigs. Escherichia Coli lipopolysaccharide (10 μg/mL, LPS) and Staphylococcus aureus endotoxin (10 μg/mL, SA) reduced eNOS protein expression and shortened the half-life of the eNOS messenger. Under basal conditions, cytosolic extracts from pericardial samples bound to the 3'-UTR of eNOS mRNA which was enhanced by LPS and SA. Proteinase K fully prevented the binding of cytosolic pericardial extracts to 3'-UTR of eNOS mRNA, suggesting the involvement of proteins that were further characterized as 60-KDa and 51-KDa proteins by cross-linking assay. Aspirin (1-10 mmol/L) restored eNOS expression in either LPS and SA-stimulated pericardial samples and reduced binding activity of the pericardial cytosolic proteins to 3'-UTR of eNOS mRNA. Indomethacin also reduced the downregulation of eNOS by LPS and diminished the binding activity of the cytosolic proteins although higher doses of indomethacin than of aspirin were needed to improve these parameters. In conclusion, eNOS protein is expressed in guinea-pig pericardial tissue. LPS and SA stimulate the binding activity of pericardial cytosolic proteins to 3'-UTR of eNOS mRNA and reduce eNOS protein expression. High doses of aspirin and indomethacin protect eNOS protein expression and reduce the binding activity of the cytosolic proteins to 3'-UTR of eNOS mRNA, suggesting an inverse association between the presence of these cytosolic proteins and eNOS expression. A better knowledge of the mechanism by which aspirin and indomethacin protects the expression of eNOS protein in the pericardium may lead to new pharmacological strategies in the prevention of the pericardial dysfunction associated with pericardial inflammation.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

P1831 Long-term experience with ICDs in the management of patients with arrhythmogenic right ventricular cardiomyopathy

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Background: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetically determined heart disease characterized by a progressive loss of right ventricular myocardium and its replacement by fibro-fatty tissue. The disease is frequently associated with life-threatening ventricular tachyarrhythmias. Therefore, therapy with implantable cardioverter-defibrillators (ICD) is considered in selected cases. However, there is limited published data concerning the role of ICD therapy in this disease in the long term.
Methods and Results: Twenty-two patients (19 male, age: 42 ± 14 years) who were diagnosed to have ARVC based on standardized criteria underwent implantation of an ICD at our institution. Indication for ICD implantation was presence of hemodynamically significant ventricular tachyarrhythmias (inducible and nonsuppressible, or associated with marked right ventricular dilatation and/or left ventricular involvement) in 20 patients (91%), and strong family history of sudden death in 2 patients. The mean follow-up period was 30 months (range: 6 - 82). Ten patients (45%) developed a total of 624 episodes. 95% of these episodes were successfully terminated by painless antitachycardia pacing therapies. Six patients (27%) received inappropriate therapies, which were due to supraventricular arrhythmias in five cases. There were two deaths; one patient died because of intractable heart failure, and another died suddenly despite delivery of appropriate ICD therapies.
Conclusion: Ventricular tachyarrhythmias occur commonly in ICD recipients who have ARVC. Antitachycardia pacing therapies can terminate the vast majority of these episodes. Inappropriate therapies are also relatively common and may complicate management of these patients. Overall, however, ICD implantation should be considered in ARVC patients with a high-risk profile.

P1832 Autosomal dominant familial left ventricular ARVC

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Background: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a heart muscle disease typically characterised by fibro-fatty replacement of the right ventricle. Isolated post-mortem cases of fibro-fatty replacement of left ventricular myocardium are reported.
Familial ARVC has been described with recurrent left ventricular involvement in only small families, with three small families linked to chromosome 2q32 by using a cumulative LOD score approach. However, cumulative LOD scores can only be used in the absence of genetic heterogeneity. We describe a single family of sufficient size to provide linkage by two-point linkage analysis with primary left-ventricular ARVC.
Methods: Detailed clinical assessment of a large pedigree of 52 individuals considered to have primary left ventricular ARVC with ECG, echocardiography, signal averaged ECG, exercise testing and Holter monitoring was performed. The index case suffered a sudden cardiac death aged 23 with post-mortem findings of fibro-fatty replacement of the left ventricular myocardium.
Results: 14/52 individuals were considered to be affected by a primary left ventricular variant of ARVC. Consistent clinical features were T wave inversion in the inferolateral leads (8 individuals) and left ventricular dilatation with an LVED>117% (6 individuals). 9 individuals had significant arrhythmia on exercise treadmill testing. 7 individuals had a positive signal averaged ECG. In addition Holter monitoring has identified frequent polymorphic ventricular arrhythmias. Segregation analysis supports an autosomal dominant mode of inheritance. Simulation with the linkage programme calculated a maximum LOD score of 3.6.
Conclusions: ARVC is an inherited disorder, with autosomal dominant disease present as both a primary right ventricular fibro-fatty replacement and left ventricular fibro-fatty replacement. Clinical manifestations of primary left ventricular ARVC are quite distinct from those in the more typical right ventricular form of the disease. T wave inversion in the right pre-cordial leads identifies individuals with the typical form of ARVC, and T wave inversion in the inferolateral leads identifies those individuals with the left ventricular variant. In addition structural alteration of the left ventricle with left ventricular dilatation with normal right ventricular measurements highlights the contrasting expression of this phenotype. It may be that the genes responsible for fibro-fatty replacement of the myocardium may not be cardiac chamber specific and may affect the right ventricle, the left ventricle or both.

P1833 Differences in the clinical expression of arrhythmogenic right ventricular cardiomyopathy in male and female patients

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Background: arrhythmogenic right ventricular cardiomyopathy (ARVC) is a myocardial disease that can lead to juvenile sudden death (SD). Although genetic studies demonstrated an autosomic inheritance, the prevalence of affected patients and SD is higher in males than females in all series.
Aim of the study: to investigate the different penetrance of ARVC in males respect with females in a series of consecutive patients affected by the disease.
Materials and methods: 195 consecutive patients diagnosed with ARVC in our center were analyzed. The diagnosis was made following the ISFC major and minor criteria. There were 145 males, 50 females, mean age 34±15 years. The clinical and instrumental findings of 50 consecutive male and female patients were evaluated. All patients underwent clinical examination, 12-lead ECG, signal averaged ECG (SAECG), two-dimensional and Doppler echocardiogram and 24 hours Holter ECG. In patients with life-threatening ventricular arrhythmias invasive cardiac examination was also carried out.
Results: Familial history of SD and/or ARVC was similar in the two groups (24% vs 20%, p=NS). Among males the percentage of competitive athletes was significantly higher (38% vs 16%, p=0.01). The right end diastolic volume was larger in males than females (86±24 ml/m^2 vs. 64±16 ml/m^2, p<0.0001) and right ventricular ejection fraction was lower (54±8% vs. 58±8%, p=0.01). Although the presence of late potentials was not significantly different in the two groups, QRS duration and filtered QRS at 25, 40, and 80 Hz filters were significantly more altered in men (101±15 vs 92±14, 131±19 vs 119±14, 124±20 vs 111±15, 112±20 vs 99±15, p=0.003, p=0.0004, p=0.0002, p=0.0003 respectively). The incidence of overall ventricular arrhythmias were similar in the two groups, however life-threatening arrhythmias (sustained ventricular tachycardia and ventricular fibrillation) were significantly more frequent in males (32% vs 14%, p=0.03).
Conclusions: the prevalence and severity of ARVC is higher in male than female patients. Environmental factors could play a role in this gender clinical difference; among these, strenuous physical activity resulted to be significantly higher in the male group. However, the possible role of endogenous factors cannot be excluded.

P1834 Diagnosis of arrhythmogenic right ventricular cardiomyopathy: standard electrocardiogram revisited

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Similar to long QT syndrome and Brugada syndrome arrhythmogenic right ventricular dysplasia-cardiomyopathy (ARVD) is thought to be a primarily electrical disease. Whether ARVD is characterised by a few ECG features as the above mentioned syndromes should be analysed retrospectively.
Results: In a cohort of 231 patients (130 males, mean age 47.6 years) with ESC/IFSC criteria of ARVD the following ECG features could be found:
Localised right precordial QRS prolongation of at least 100 msec in 227 patients (98%), right precordial T inversions in 134 cases (58%), complete right bundle branch block (RBBB) in 18 patients (8%), incomplete RBBB in 28 patients (12%), "pseudo" incomplete RBBB (no S wave in V5 + V6) in 6 cases (3%), R > S wave amplitude in V2 with QRS interval of at least 110 msec in 29 patients (13%), localised QRS prolongation in inferior leads in 49 patients (21%), right precordial ST elevation in 62 cases (27%) and loss of R wave in V1 - V3 in 12 cases (5%).
In conclusion, the variety of ECG findings demonstrates that ARVD is not only an electrical disease but is characterised by different morphological changes of the right and in about 50% of cases the left ventricle. Similar to long QT syndrome and Brugada syndrome a central ECG finding - localised right precordial QRS prolongation of at least 100 msec - can be found in ARVD cases and contributes significantly to the diagnosis of ARVD.

P1835 Clinical presentation of index arrhythmogenic right ventricular cardiomyopathy cases: a tertiary centre experience

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Introduction: The clinical features of arrhythmogenic right ventricular cardiomyopathy (ARVC) include arrhythmia, heart failure and sudden cardiac death. We studied the mode of clinical presentation and results of non-invasive cardiac evaluation using ARVC task force criteria, in a consecutive series of index cases.
Methods: ARVC index cases were identified at our centre, referred from other centres or discovered at autopsy. Family members were interviewed about symptoms among the deceased cases. Live cases underwent historical assessment, 12-lead and signal-averaged ECG, 2-D echo, Holter monitoring and exercise testing. The families of these cases were offered cardiac evaluation.
Results: Of 75 index cases (age 31 ± 11 years), 44 (59%) presented with sudden cardiac death (SCD) and were diagnosed at autopsy. They presented at a younger age than the live cases (age 28 ± 9 v 36 ± 13 years; p<0.005) and the majority were male (71%). Six (14%) of this group experienced syncope one month prior to their death. Therefore, 38 (51%) cases had SCD as their initial clinical feature with no preceding symptoms. Live cases presented with palpitations/pre-syncope 16 (53%), syncope 10 (33%), VF arrest 2 (7%)and heart failure 2(7%).
Presence of ARVC task force criteria are summarised below.

Table showing prevalence of criteria

Task Force Criteria	Prevalence
T-inversion in leads V1-3	20 (64%)
Epsilon waves	1 (3%)
QRS duration>110 milliseconds	6 (19%)
Abnormal signal-averaged ECG	18 (58%)
>1000 ventricular ectopics/24 hours	13 (42%)
Major RV echocardiographic abnormalities	16 (52%)
Minor RV echocardiographic abnormalities	15 (48%)
Left bundle branch block VT	29 (sustained 70%, NSVT 23%)

Conclusion: The commonest presentation of index ARVC cases to our centre was with SCD, presenting at a younger age compared to other clinical features. The majority of live cases presented with features of ventricular arrhythmias. ARVC task force criteria involve routine cardiac tests, most being available at secondary and tertiary centres. Our experience shows that they should enable better diagnostic success.

P1836 Evaluation of electrocardiographic and echocardiographic diagnostic criteria for ARVC in Naxos genotyped population

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Background The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) is based on established criteria by ESC/ISFC. Naxos disease is an autosomal recessive ARVC, 100% penetrant by adolescence due to a deletion mutation in plakoglobin. Genotyped population of all Naxos disease families was available to evaluate the sensitivity and specificity of electrocardiographic and echocardiographic diagnostic criteria.
Methods Resting 12-lead ECG and two-dimensional echocardiography were studied in all adult homozygous carriers for plakoglobin mutation (13 men and 13 women, age 42.5±19 years) and in 35 homozygous for normal allele (12men and 23 women, age 41.2±14 years) from 12 families. T wave inversion, QRS complex duration, QRS dispersion (QRS width in V1-V3 minus that in V6), epsilon waves and right ventricular (RV) dimensions/wall motion were evaluated using a standard protocol. Sensitivity and specificity analysis was applied using the receiver operating characteristic curve in order to identify optimal cut-off points for the evaluated diagnostic parameters.
Results Sensitivity and specificity of ECG and echocardiographic findings are presented in the table.

	Sensitivity	Specificity
T wave inversion in V1	88%	22%
T wave inversion in V2	81%	79%
T wave inversion in V3	73%	92%
QRS width > 110ms in V1-V3	73%	100%
QRS dispersion > 25ms	58%	91%
Epsilon waves	54%	100%
Ventricular extrasystoles (LBBB)	88%	94%
RV outflow tract diameter > 32.5mm	85%	94%
RV inflow tract diameter > 35.5mm	89%	85%
RV wall motion abnormalities	100%	100%

Conclusions T wave inversion in V2 or V3, QRS complex prolongation in V1-V3, ventricular extrasystoles of RV origin, as well as RV dilatation and wall motion abnormalities seem to be the best diagnostic criteria in this ARVC group. QRS dispersion and epsilon waves although specific for the disease they show rather low sensitivity.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR – TECHNICAL ASPECTS

1889 Detection of tachyarrhythmia with a dual chamber defibrillator connected to a defibrillation lead with a free-floating atrial bipole

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The aim of the study was to assess the sensitivity and specificity of new modified dual chamber cardioverter defibrillator (ICD) connected to a defibrillation lead with a free-floating atrial bipole. The study included 72 patients (63 ± 10 years, ejection fraction 38 ± 14%, coronary heart disease n = 61) who received as a first implant the dual chamber ICD Deikos A + and the single-coil defibrillation lead with a free-floating atrial bipole Kainox VDD (Biotronik). Indications for ICD implantation were ventricular tachycardia in 45, ventricular fibrillation in 18, and other indications in 9 patients. The ICD has a more sensitive atrial detection channel and enhanced detection algorithms for the discrimination between atrial and ventricular arrhythmia. At discharge, the enhanced detection algorithms were programmed on. There are two lead models with 15-cm and 17-cm distance between electrode tip and atrial dipole.
Results: A lead with a 17-cm distance was implanted in 61 and with 15-cm distance in 11 patients. Procedure duration was 103 ± 43 minutes. Induced ventricular fibrillation was successfully terminated as recommended with maximal 20 Joule in all patients. Unfiltered P-wave amplitude at implantation was 1.0 ± 1.0 mV. Filtered P-wave amplitude was 5.2 ± 1.6 mV at implantation, 4.6 ± 1.7 mV at month 1, 4.6 ± 2.0 mV at month 3, and 5,0 ± 1.8 mV at month 6. There were 125 spontaneous episodes during 4.5 ± 3 months follow-up with 18 episodes of ventricular fibrillation, 43 episodes of ventricular tachycardia, 30 episodes of supraventricular tachycardia, and 34 episodes of sinus tachycardia. The ICD correctly detected all episodes of ventricular fibrillation, 98% of the ventricular tachycardia episodes, 89% of the supraventricular tachycardia episodes, and 97% of the sinus tachycardia episodes.
Conclusions: The dual chamber ICD connected to the defibrillation lead with a free-floating atrial bipole detected due to the more sensitive atrial channel P-wave signals with a high amplitude. The device had a sensitivity of 98% and specificity of 91% for the detection of tachyarrhythmias.

1890 Programming assistant for implantable cardioverter/defibrillators: multi-centric evaluation of a rule-based expert system

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Modern implantable cardioverter/defibrillators (ICD) put growing demands on the physician, as their complexity requires increasing knowledge and effort for handling these devices. To overcome this development a Programmer-Assistant (PA) was developed, which transfers the clinical data entered by the physician into a complete parameter set for the programming of a dual-chamber ICD (Tachos DR, Biotronik) for DFT testing (DFT-P) and the first permanent programming after implant (First-P).
Methods: 168 patient files from routine implantations were evaluated by ICD experts of 15 centers in USA, UK and Germany. After entering the data in the PA the experts evaluated, separately for DFT-P and First-P, each single parameter and the parameter set as a whole.
Results: 168 patients (136 m, 32 f), age 66 ± 12 years, ejection fraction 30 ± 12%, cardiac disease: coronary artery disease 119, dilated cardiomyopathy 21, valvular 20, Long-QT syndrome 3, hypertrophic cardiomyopathy 2, idiopathic ventricular fibrillation 3.
The evaluation of the single parameter is summarized in the table. The DFT-P was accepted as a whole program in 159 cases (94,6%), not accepted in 9 (5,4%). For First-P the result was 157 (93,5%) vs. 11 (6,5%) case. None of the DFT-P and First-P was considered harmful. The disapproval of the 9 respectively 11 cases was based only on center-specific preferences. The PA was adapted to include these preferences.

Single Parameter Evaluation

mean ± SD	Identical	Acceptable	Not Acceptable	Harmful
DFT-P	98,4 ± 1,8	1,0 ± 1,4	0,5 ± 1,2	0,0 ± 0,0
First-P	96,1 ± 3,7	2,4 ± 2,2	1,5 ± 2,2	0,05 ± 0,2

The percentage of parameters in each category per patient is averaged over all patients.

Conclusion: The PA, which allows the physician to program ICDs directly with clinical data, is a safe method to simplify the programming of modern complex ICDs.

1891 Development of a rechargeable implantable cardioverter-defibrillator: first results of in-vitro measurements

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Present ICD-systems use a conventional dry battery as energy source. Therefore most often life span of this system is determined by the capacity of the battery, which amounts depending upon demand 3-5 years. If the battery is exhausted, the entire device must be exchanged. An expensive operation with many physical and psychological risks and side effects for the patient is the consequence, which can significantly affect the quality of life. If the energy source in these systems would be rechargeable, most of these exchange operations could be omitted.
Methods: The project deals with recharging of batteries through the intact skin via a magnetic field. The aim of the study is to improve the energy transfer into the ICD without any tissue damage. We started with simulations with finite-element-programs to optimize the magnetic field dependent on different coil forms. Furthermore, in-vitro-measurements were carried out to identify the appropriate frequency of the magnetic field. An automatic compensation of variable boundary conditions (e.g. tissue thickness) was tested. The Ventak Prizm II (Guidant, MN) widened with a receiving coil for energy transmission and a charging electronic was used as prototype.
Results: A large coil around the can for energy receiving was identified having the best transmitting results. The higher the field frequency the higher the absorption of the housing of the ICD that could be estimated at 16dB at 100 kHz. The optimum frequency for energy transmission is 100 kHz. There was no significant heating of tissue between both coils.
Conclusion: Using optimized parameters, transmission of energy intended to recharge batteries of ICDs is possible without unacceptable heating of the surrounding tissue.

1892 Efficacy and reliability of transvenous ICD-lead extraction using mechanical and electrosurgical devices

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Introduction: Defect ICD- leads should be removed before implanting new ones as electromechanical interactions between defibrillation coils may produce oversensing and unexpected shock delivery.
Material and method: Since march 1995, 44 defect transvenous ICD- leads had to be removed at the University Hospital of Tübingen. Mean age of patients was 59.7 years (range 20 to 81), gender 38 males and 6 females, 34 pectoral and 10 abdominal devices. Mean lead age was 42.1 months (range 1 to 109) including 18x Transvene- (Medtronic), 18x Endotak- (CPI/Guidant), one Intermedics- and one Teletronic- lead. Extractions were performed in a thoracic- and heart- operation theatre with HLM stand-by and TEE- monitoring. Clinical evidence of lead defects were oversensing in 31 cases, exitblock in 9 cases, Twiddler syndrome in 3 cases and one infection. Vascoextor stilett (Vascomed) alone was used in 5 patients, 4 times in combination with a plastic sheath (COOK), Cook liberator stilett (or stilett 0.017-0.019) combined with plastic sheath seize 11,5-13 Fr. in 24 patients, 4 times electrosurgical dissection sheath (EDS COOK), and in 7 cases without supporter devices (lead age < 6 months).
Results: One Endotak lead (age 77.6 months) could not be extracted by mechanical devices without EDS support. Thoracotomy was necessary to remove the distal defibrillation coil from the embedding scar tissue in the right ventricular area. In one case the plastic sheath perforated the wall of the right ventricle during contermove with the liberator- stilett (one of the first extractions). Resuscitation, thoracotomy and closure of the defect was successful. In all other cases the transvenous approach for lead extraction was successful, in four of these cases electrosurgical dissection sheaths were necessary. New leads were implanted during the same session using Seldinger-technique.
Conclusions: Transvenous lead extraction may be performed successfully and safely in almost all cases. Extractions should be done in an operation theatre with availability of thoracic and heart surgery, HLM stand-by and TEE monitoring. Plastic sheaths should carry x-ray dense markers to improve visibility during fluoroscopy.

1893 Excimer laser sheath is emerging as a safe and effective alternative for the extraction of complicated pacemaker and ICD leads

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Background: Historically, conventional techniques for extraction of pacemaker and defibrillator leads have resulted in a variety of complications. When thoracotomy procedures were mainstay of lead extraction management, extraction procedures were reserved only for the most life threatening situations. With the advent of new extraction equipment like laser sheath, the risk/benefit analysis allows the physician to utilize extraction techniques more readily.
Purpose: The purpose of the study was to determine the safety and efficacy of excimer laser sheath for complicated pacemaker and ICD leads.
Method: Prospective data analysis was done for the extraction of pacemaker and defibrillator leads at Hahnemann University Hospital. Only patients who could not be extracted with conventional techniques were selected.
Results: 450 patients with 802 leads were referred to our center for the extraction of pacemaker and defibrillator leads during the period Jan.1991-Nov. 2001.Laser-assisted extraction techniques were utilized in 65 patients with 92 leads. The study population included 50 male and 15 female patients with mean age of 60±14 years (range 30-90 years). The indications for these extractions were malfunction (47%), infection (44%) and others (12%). Laser sheath was undertaken if conventional techniques failed. The mean implant duration was 105 months (range 2 - 228 months) and the mean extraction time excluding the reimplantation was 40 minutes (range 10 - 120 minutes.) Complete lead extraction was achieved in 98% patients. All attempted reimplantation procedures was successful. The overall complication rate was 5% with cardiac tamponade being the most significant complication.
Conclusion: Excimer laser sheath appears to be safe and effective technique for the extraction of heavy fibrotic pacemaker and defibrillator leads. Although with high success rate it was also associated with significant complications. These complications were most likely due to the increased chronicity and complexity of leads extracted by this method.

1894 Rhythm discrimination in single and dual-chamber implantable cardioverter defibrillators: usefulness of QRS analysis by morphology discrimination

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Morphology Discrimination (MD) is a rhythm discriminator based on the analysis of QRS complex morphology.
The clinical relevance of MD in improving rhythm discrimination in combination with other discriminators (i.e. Sudden Onset and Stability) was assessed in patients (pts) implanted with a cardioverter defibrillator (CD). Two series of pts were analysed: 26 pts with a single-chamber CD (mean follow up 29 months) and 25 pts with a dual-chamber CD (mean follow up 14 months). All detections were reviewed and classified. Sensitivity (SE) and Specificity (SP) in rhythm discrimination were evaluated according to various potential diagnostic settings for ventricular tachycardia (VT) diagnosis (i.e. with "any" or "all" the discriminators indicating VT). In single-chamber CDs also the diagnostic setting with "2 out of 3" discriminators was considered. The net advantage of MD was evaluated by assessing the diagnostic performance without use of MD.
Overall 400 detections (184 VT, 25 ventricular fibrillation [VF] and 191 supraventricular tachyarrhythmias [SVT] were analysed in single-chamber CDs and 645 (234 VT, 397 SVT and 14 VF)in dual-chamber CDs. The results are shown in the table.

Diagnostic setting		Single-chamber CD		Dual-chamber CD	
		with MD	without MD	with MD	without MD
"Any"	SE	100% (184/184)	100% (184/184)	100% (234/234)	
	SP	37.7% (72/191)	41.4% (79/191)	73.5% (292/397)	
"All"	SE	73.9% (136/184)	75.0% (138/184)	98.7% (231/234)	98.7% (231/234)
	SP	94.2% (180/191)	94.2% (180/191)	90.9% (361/397)	74.7% (296/397)
"2 out of 3"	SE	97.3% (179/184)			
	SP	79.1% (151/191)			

Legend: SE = sensitivity; SP = specificity.

In conclusion, use of MD in appropriate combination with Sudden Onset and Stability allows to obtain in single-chamber CDs a SP of 79.1% with maintenance of 97.3% of SE; thus, in single-chamber CDs the net advantage of MD is an increase in SP without an harmful drop in SE. In dual-chamber CDs, SE is high (98.7-100%) both with and without MD; however, use of MD allows an improvement in SP from 74.7% to 90.9%. Therefore, the implementation of MD implies a net advantage in rhythm discrimination, even when more traditional rhythm discriminators (i.e. Sudden Onset and Stability) are considered.

SYNCOPE – TILT TEST AND LONG-TERM OUTCOME

1895 Head-up tilt test potentiated with nitroglycerin. Which is the optimal duration of the test after the administration of the drug?

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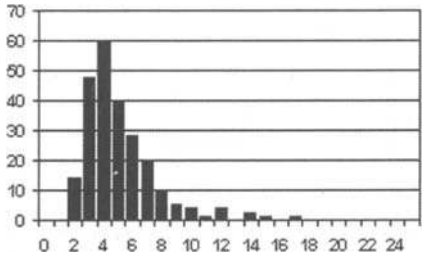
Numerous variations in the methods used for tilt-table testing potentiated with nitrates have been reported. After the administration of nitroglycerin, between 10 and 25 minutes of continued tilting have been recommended. The objective of this study is to assess the optimal duration of the pharmacologic phase of the tilt-table test potentiated with sublingual administration of nitroglycerin spray (NTG-TT).

Methods: The records of 470 consecutive NTG-TT performed in 379 patients were reviewed. Our protocol consists of a 20-minutes drug-free phase at 60°. If syncope did not develop, 400 μg of sublingual nitroglycerin spray were administered and the patient continued to be tilted for a further 25 minutes. The test results and time to a positive response were analyzed.

Results: The result of NTG-TT was positive in 269 procedures, most of them after nitroglycerin administration (238, 88.5%). The mean time to a positive response was 10.5 ± 7.2 min and 5.1 ± 2.4 during the control and pharmacologic phases respectively. Most positive responses concentrated between 3 and 5 minutes after drug administration. The time to syncope after nitroglycerin administration was superior to 10 minutes in 5 patients, and to 15 minutes in only one.



Time to a positive response.

Conclusions: The duration of the pharmacologic phase of tilt-table testing potentiated with sublingual nitroglycerin spray may be reduced to 15 minutes without loss of sensitivity. A further reduction to 10 minutes would decrease the rate of positive responses only by a small amount and may be considered acceptable from a clinical perspective.

1896 Three to five year follow-up after a positive tilt-table test for neurocardiogenic syncope in Israeli soldiers

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Neurocardiogenic syncope (NCS) is the most common cause of syncope in young otherwise healthy pts, can be readily diagnosed with tilt-table testing, and is usually responsive to therapy with either medications or pacemakers. However, information on the natural history of the disease and thus the duration that treatment is required is limited; that most pts. with NCS are young suggests that pts. may outgrow the disorder with time.

To examine the long-term course of NCS, we performed telephone interviews in 45 young Israeli solders (age 20 ± 1.6 y, range 18 to 24, 67% male) a mean of 4.0 ± 0.7 y (range 3 to 5.5 y) after a positive tilt test diagnostic for NCS (defined as syncope or near-syncope associated with both bradycardia and hypotension). The pts. had a mean of 9 ± 8 (range 2 – 30) prior syncopal episodes. Of the 45 pts., 31 had a positive baseline tilt test (30 min, 70° upright tilt) while the remaining 14 pts. had positive tests only with isoproterenol provocation (2 mcg/min for 10 min). (161 other soldiers with recurrent syncope tested during the same time period had negative tilt tests and were not included in the study, and 3 pts. with positive tilt tests were unavailable for interview). All but 3 pts were treated with drug therapy (beta-blockers used in 39 pts., florinef in 3, and serotonin-uptake inhibitors in 8) and re-assessed with repeat tilt-table tests until a negative test was achieved; 35 pts. were treated successfully with a single drug while 7 pts. required combination therapy. To avoid bias, pts. were not followed by us but rather returned to their regular army physicians and told to continue on the drug therapy. We found only 2 pts. were still taking medication, 1 pt. (2%) still reported frequent syncopal or near-syncopal episodes, 4 pts. (9%) had rare symptoms (defined as no more than 1 syncopal episode per year for each of the past 2 years) while the remaining 38 (84%) were symptom - free off of medications. Some pts. attributed relief of their symptoms to discharge from the army.

We conclude that NCS, at least in young pts., even when confirmed by a positive tilt-table test, is often a self-limited disorder, perhaps stress-related or situational in nature, and that the overwhelming number of pts. are asymptomatic and stop taking medications within 1 - 2 years. This study has obvious implications in choosing therapy for NCS pts. (such as drug therapy vs. pacemaker therapy), prescribing the duration of therapy, and in providing recommendations regarding occupation and restrictions on driving or athletic activity.

1897 Clomipramine versus conventional tilt table test: a prospective, randomized study, comparing sensitivity and specificity between the two tests

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Central serotonergic activation participates in the pathogenesis of neurocardiogenic syncope. In this study, we assessed the sensitivity and specificity of the head-up tilt test with central serotonergic activation, using the serotonin reuptake inhibitor clomipramine (CL-HUT). We also compared this test with the conventional 60° head-up tilt test (CON-HUT) with or without isoproterenol.

Methods: We prospectively studied 126 patients (pts) with a positive history of recurrent VVS (mean age 41±16 yrs, 66 women, 60 men) and 27 healthy control subjects (mean age 46±15 yrs). Both pts and controls underwent sequentially a CL-HUT and a CON-HUT, in random order. During CL-HUT, clomipramine was infused (5 mg in 5 min) at the beginning of the 20 min lasting head-up tilting. CON-HUT was performed at 60° for 30 min and if negative, isoproterenol infusion followed (2-4 μ/min, for 10 min). A 24 hours interval has interspersed between the two tests.

Results: (Table, pos: positive, neg: negative).

The sensitivity and specificity of CL-HUT was 83% and 93% respectively, while for CON-HUT it was 41% and 96%. As shown in the table, the sensitivity and specificity of each test was not dependent on whether it was the 1st or the 2nd one in the randomized order.

	pts			controls		
	1st test	2nd test	total	1st test	2nd test	total
CL-HUT pos	51 (81%)	54 (86%)	105 (83%)	1 (8%)	1 (7%)	2 (7%)
CL-HUT neg	12 (19%)	9 (14%)	21 (17%)	12 (92%)	13 (93%)	25 (93%)
CON-HUT pos	27 (43%)	25 (40%)	52 (41%)	0 (0%)	1 (8%)	1 (4%)
CON-HUT neg	36 (57%)	38 (60%)	74 (59%)	14 (100%)	12 (92%)	26 (96%)

Conclusion: Clomipramine infusion improves the diagnostic value of HUT compared to conventional test, without a loss of specificity. The reproducibility of CL-HUT remains high, independently on whether it is performed as the 1st or the 2nd HUT.

1898 Syncope in young competitive athletes: prevalence, clinical correlates and long-term outcome

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Between January 1989 and September 2001, 7568 consecutive young competitive athletes (67,9% males, mean age 16 yrs) underwent a preparticipation cardiovascular screening. Syncopal spells (at least one episode) were reported by 474/7568 athletes (6,2%; mean number of syncopal episodes: 1,2). Syncope was unrelated with exercise in 411/474 athletes (86,7%), post-exertional in 57/474 (12,0%) and exertional in 6/474 (1,3%). In all athletes with non-exertional and post-exertional syncope, the episodes showed the typical clinical features of vasovagal fainting and cardiovascular screening was negative. Athletes with exertional syncope underwent further testing (echocardiography, Holter ECG and maximal exercise testing). Such work-up showed normal results in 4 cases. As to the remaining 2 athletes, echocardiography allowed the diagnosis of hypertrophic cardiomyopathy in 1 case, while repeated episodes of non-sustained ventricular tachycardia were noted during Holter ECG in the other. Both of these athletes were disqualified from further participation in competitive sports. Athletes were followed for a mean period of 84,6 months. Follow-up data were available for 6887 athletes (91,0%), including all subjects who had reported syncopal spells during the initial evaluation. During the follow-up period, 58/411 (14,1%) athletes with previous non-exertional and 9/57 (15,7%) with previous post-exertional syncope showed recurrence of syncope. None of the athletes who had reported exertional syncope had any recurrence of syncope during the follow-up period. Moreover, 1,0% (66/6413) of the athletes who did not report any syncopal spell at the initial evaluation had a non-exertional syncopal episode during the follow-up period. No other major adverse cardiovascular event was noted during the follow-up period. In this study, both non-exertional and post-exertional syncopal spells in athletes were not associated with abnormal cardiovascular findings. Exertional syncope is a rare event in young athletes, but may be associated with significant cardiac abnormalities requiring disqualification.

1899 Dysfunctional baroreflex regulation of sympathetic nerve activity in patients with vasovagal syncope

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Background: The interplay of resting muscle sympathetic nerve activity (MSA) and baroreceptor reflex in patients with vasovagal syncope remains still elusive. Hence, the aim of the present study was to investigate MSA, baroreceptor sensitivity (BRS), heart rate and blood pressure in resting condition and under orthostatic stress in patients with vasovagal syncope.
Methods: MSA was measured using microneurography at rest and during lower body negative pressure (LBNP) to mimic orthostatic stress in patients with a history of vasovagal syncope (n=7) and age-machted healthy volunteers as control (n=7). Heart rate and blood pressure were simultaneously recorded. BRS was calculated with the spectral technique (a coefficient).
Results: Resting MSA in the syncopal group was significantly increased vs. control (26.6±11.0 vs. 44.0±7.9 bursts/min, P=.005). Activation of MSA during orthostatic stress in the syncopal group was significantly blunted (15.2±4.6 vs. 4.6±5.3 bursts/min at LBNP -50 mmHg, P=.0046). The baroreceptor sensitivity was significantly reduced under supine resting conditions and also under orthostatic stress in the group of the patients (7.98 ± 2.58 vs. 13.42 ± 3.48 ms/mmHg, P=.0116; 6.55 ± 2.16 vs. 13.86 ± 4.77 ms/mmHg, P=.0066). BRS remained stable vs. baseline within the groups under LBNP.
Conclusions: This study shows (1) that resting sympathetic nerve activity is increased in patients with vasovagal syncope and (2) baroreflex regulation during orthostatic stress is blunted in these patients, thus leading to impaired MSA adaptation. These results provide the rationale for pharmacological approach to modulate barorecetor sensitivity in treatment of neuromediated syncope.

1900 Value of subcutaneous implantable loop recorder for detection of paroxysmal asystole underlying unexplained syncope

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Introduction: Intermitent cardiac arrhythmias underlying syncope may remain undetected with convential methods. Continuous cardiac monitoring with a subcutaneous implantable loop recorder (ILR) has been introduced as a new diagnostic tool. We evaluated it's diagnostic yield in patients with unexplained syncope.
Methods: Between 1998 and 2000, 26 patients with undiagnosed syncope received an ILR after a negative complete evaluation that included ECG, carotid sinus massage, 24-hour Holter recording, echocardiogram, and electrophysiological study (EPS). The mean age was 58±16 yrs, 16 were male, and 5 had suffered trauma due to the event. Patients were included irrespective of the result of a head-up tilt test(HUTT)because of the severity of symptoms. The ILR (Reveal 9525/9526) was implanted subcutaneously in the left subclavicular, submammary, or subcostal position, and patients were instructed in the use of manual device activation. Follow-up was performed every 3 months or after events.
Results: During a follow-up of 14±5 months, 16 of the 26 patients experienced a total of 44 events. The majority of events consisted of palpitations or dizziness without syncope and the ILR was useful to rule out arrhythmias. True syncope occurred in only 10 patients(38%)during follow up. In 5 of them, the ILR recorded slowing of sinus rhythm followed by asystole and syncope, suggesting a neurally-mediated event. The previous cardiac workup had demonstrated one patient with an old inferior myocardial infarction, one with chronic AF, one with RBBB and LAFB, one with a nocturnal pause < 2 seconds on Holter, and one with a completely normal screening. All patients with a recorded asystole were treated with a pacemaker. In the other 5 patients with recurrence of syncope, no arrhythmias were documented. Two patients were found to have epilepsy while in the remaining 3 patients no diagnosis could be established. Of interest, the HUTT was positive in 5 of the 16 patients that did not have a renewed episode of syncope, but negative in 9 of the 10 patients that did have a true syncopal recurrence. In all patients EPS was normal and no arrhythmias were inducible, despite structural heart disease in some. There were no device related adverse effects during follow-up.
Conclusions: The ILR is a safe and simple diagnostic tool to detect cardiac asystole in selected patients with unexplained syncopal events, and it helps in ruling out arrhythmic causes in others. The HUTT did not predict paroxysmal asystole in this group of patients, in spite of the suspected neurocardiogenic origin.

SMOKING IN PATIENTS WITH ISCHAEMIC HEART DISEASE: RISK ASSESSMENT AND TREATMENT

1922 In the life course, CVD incidence and prevalence is smaller among smokers than among non-smokers: a multistate life table analysis of Framingham

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Background: The thesis of compression of morbidity suggest that life style modification, with smoking as example, can compress morbidity: incidence can be postponed, but mortality can not decrease beyond natural limits. We investigated this hypothesis by studying cardiovascular morbidity of smokers and non-smokers in the long lasting cohort of the Framingham Heart Study.
Methods: Individual life courses are constructed by estimating annual age specific transition probabilities in multistate life tables describing the states 'free of CVD, CVD, death'. Similar life tables are constructed for CHD, MI, stroke and CHF. Non smokers are defined as participants where smoking was recorded in less than 20% of the available biannual surveys, smokers are participants where smoking was recorded in more than 80% of the surveys.
Results: 70.0% of 5057 persons included had less than 20% of the exams missing. Respectively 24% and 48% of the men were defined as non smokers and smokers, compared to 59% and 25% of the women.
Male non smokers had consistently higher probabilities than smokers of ever having CVD (+1%), coronary heart disease (+4%), MI (+7%), CHF (+5%), but a lower probability of stroke (-10%). Female non smokers had higher probabilities than similar smokers of ever having CVD (+3%) and coronary heart disease (+5%), but a similar probability of MI, and lower probabilities of CHF (-2%) and stroke (-1%).
Male non smokers lived considerably longer with cardiovascular disease: + 2.1 y (CVD), +1.2 y (coronary heart disease), +0.6 y (MI), +0.5 y (CHF) and +0.4 y (stroke). Female non smokers lived longer with cardiovascular disease too, but not with all types: +1.7 y (CVD), + 1.6 y (coronary heart disease), + 0.3 y (stroke), but - 0.1 y (MI and CHF).
The main reason of these apparently surprising results is that male non-smokers lived 7.4 years longer than smokers, but 'only' 5.4 years longer free of CVD. Female non-smokers lived 6.4 years longer, and 4.8 years longer free of CVD.
Conclusion: Ageing causes the paradoxes of health: the better our health, the longer we live, the more we are exposed to age related disorders, the more we need care. The assumption that life style modifications might save health care needs is naive and dangerous to health care budgets. For 2 years added with cardiovascular disease (many of which are asymptomatic), non smokers live 5 years more free of disease. This is sufficient foundation for an anti tobacco policy, as the aim of public health is not to save money, but to save lifeyears.

1923 Smoking and cardiovascular risk following myocardial infarction

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Background: Smoking is an important risk factor for the development of cardiovascular disease, especially in young patients. However, these patients paradoxically have favourable outcomes compared to non-smokers. Smokers may have less complicated coronary lesions more susceptible to thrombolysis, have a higher incidence of inferior infarction and are generally younger.
Methods: The OPTIMAAL trial compared the effects of losartan and captopril in high-risk patients following AMI. The primary endpoint was all-cause mortality. A total of 5477 patients were randomised from 7 Western European Countries. 67.5% of the patients were smokers or former smokers at randomisation. We assessed all-cause mortality in patients with complicated MI with regard to smoking status and age.
Results: A total of 5477 patients were included in the trial and 926 deaths have occurred. Current smokers had 41% lower risk of death (11.6% vs 19.5%) and 27% lower risk of reinfarction (8,5% vs 11,6%) than other patients. Current and former smokers had 26% lower risk of death (15.9% vs 18.9%) and 18% lower risk of re-infarction (9.9% vs 12.1%). However, after stratifying by age, smoking was associated with an unfavourable outcome. In patients < 60 years, non-smokers had 16% lower risk of death - in patients from 60-69 years, non-smokers had 18% lower risk of death - in patients >70 years, non-smokers had a mortality similar to current/previous smokers.

All cause mortality

Age group	Current/former smokers	Non-smokers
All	15,9%	18,9%
<60 yrs.	6,8%	5,7%
60-69 yrs.	11,3%	9,3%
>69 yrs.	27,6%	27,1%

Conclusion: It has been reported that smokers apparently have lower rates of mortality and better short-term outcomes than non-smokers following MI. We demonstrate that by stratifying patients into age groups, without correcting for other comorbidity or risk factors, the apparent increase in all-cause mortality in the non-smoker group is explained by the fact that the smokers are generally younger with a better prognosis due to their age. Previous and current smokers had slightly higher mortality during the trial when the data is age-adjusted.

1924 Smoking cessation significantly attenuates sudden cardiac death risk in patients with stable angina and/or healed myocardial infarction

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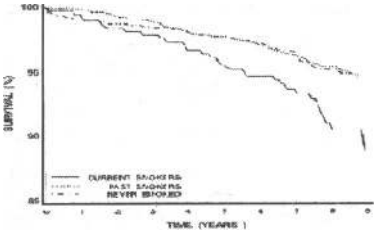
Background: The aim of this study was to evaluate the impact of current cigarette smoking and smoking cessation on sudden cardiac death (SCD) risk in patients with coronary artery disease (CAD).
Methods: We prospectively studied 3,122 patients with a previous myocardial infarction or stable angina who participated in the Bezafibrate Infarction Prevention (BIP) trial. Three hundred and seventy patients were active smokers at randomization and throughout the study period; 1,821 patients had quit smoking before inclusion in the study; 931 patients had never smoked. We compared the incidence of SCD in the 3 groups over a mean follow-up period of 8.2 years.
Results: In current smokers, 30 sudden deaths occurred (8.1%), whereas 83 sudden deaths occurred in patients who had quit smoking (4.6%) and 43 cases of SCD in patients who had never smoked (4.6%, p=0.014). In multivariate analyses, current smoking was associated with a significant increase in the risk of SCD (hazard ratio - 2.47, 95%CI 1.46-4.19). Patients who had stopped smoking had no significant increase in the risk of SCD compared to patients who had never smoked (hazard ratio - 1.06, 95%CI 0.70-1.62). Kaplan Meier survival curves (see figure) showed that After 8.2 years, the estimated rate of survival free of SCD was 95% for past smokers and never smokers and 89% for patients who continued to smoke (p=0.006)
Conclusions: We conclude that current cigarette smoking is a powerful independent predictor of SCD risk in patients with CAD. Patients who quit smoking experienced a significant reduction in SCD risk. Thus, efforts to reduce the burden of mortality from SCD in patients with CAD should include vigorous smoking cessation strategies



Kaplan-Meier survival curves.

1925 Impact of smoking status on outcomes in acute coronary syndromes: the ex-smokers' paradox

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Epidemiological data describe a smokers' paradox: younger age, yet better survival for smokers in the setting of ST-elevation myocardial infarction (STEMI). Data on the whole range of acute coronary syndromes (ACS): STEMI, non ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) are lacking.
Methods: The Global Registry of Acute Coronary Events (GRACE) collects data from 10000 ACS cases in 14 countries annually. Treatment and outcome of 15434 patients were analyzed in the STEMI, NSTEMI, and the UA groups.
Results: Smokers (S) more frequently presented with an STEMI (45.7%) than former smokers (FS) (27.3%) and non-smokers (NS) (29.8%). Smokers were mostly males, younger, and more aggressively treated than the FS and the NS in the three groups of ACS.
The in-hospital mortality rates were higher in NS compared with FS and S in each of the three groups of ACS. The multivariate logistic analysis in the ACS patients showed that the in-hospital mortality rate was significantly lower for S (3.3%) and FS (4.3%), but after adjustment for age this benefit only remained for the FS group(OR 0.78).

Smoking status and outcomes in ACS

	STEMI			NSTEMI			UA		
	S	FS	NS	S	FS	NS	S	FS	NS
N	1898	1248	2000	1096	1446	1983	1161	1876	2726
Age median y	56.2	66.4	71.3*	57.9	69.3	72.5*	56.6	66.4	70.2*
Males (%)	81.6	82.0	55.2*	78.2	80.2	50.6*	75.1	75.7	47.5*
History of PCI/CABG (%)	6.5	16.4	9.3*	15.6	30.2	20.6*	22.1	43.4	30.9*
Cath (%)	60.1	60.3	51.4*	59.6	58.4	50.1*	46.8	46.3	38.9*
PCI (%)	44.5	42.4	37.6*	32.9	28.9	26.8*	25.2	19.3	16.3*
Lytics (%)	53.6	42.3	39.9*	6.7	3.1	3.6*	7.4	3.0	3.5*
GP IIb/IIIa (%)	26.9	27.7	24.3	25.6	22.5	20.1*	11.1	7.3	7.5*
Death (%)	3.7	6.5	11.4*	3.3	5.4	6.0*	2.7	1.9	3.8*
Major bleed (%)	3.5	5.2	5.4**	3.0	4.8	4.7**	2.5	2.4	2.2

*Statistically significant at a = <0.001; **Statistically significant at a = <0.05. S = smoker; FS = former smoker; NS = non-smoker; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting

Conclusion: Survival benefits for smokers in the setting of ACS can be attributed to younger age and the resultant more aggressive treatment strategies. The reasons for a reduced mortality in ex-smokers remain to be elucidated.

1926 Zyban™ is an effective and well tolerated aid to smoking cessation in smokers with cardiovascular disease – 12 month follow-up phase data

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Cigarette smoking increases cardiovascular disease (CVD) morbidity and mortality, however patients with CVD who quit smoking significantly reduce their risk of subsequent cardiac events and death(1). The OBJECTIVE of this study (ZYB40014) was to demonstrate the efficacy (smoking abstinence) and tolerability of Zyban™ (bupropion SR) compared to placebo in a population of smokers who have CVD, and this abstract details new 12 month follow-up phase data.

Methods: 629 smokers with a history of myocardial infarction, angina, cardiac procedure, heart failure or peripheral vascular disease who were motivated to quit and smoked > 10 cigarettes/day were randomised (1:1) from 28 centres across 10 countries. Subjects received Zyban™ 150mg twice daily or placebo for 7 weeks as out-patients with weekly motivational support. Follow-up visits were attended up to 52 weeks.

Results: Baseline characteristics were similar between treatment groups and subjects had a mean smoking history of 49.6 pack years (S.D. = 25.4). Four week continuous abstinence (weeks 4-7) was more than double in the Zyban™ group, 43%, versus placebo, 19% ($p<0.001$, odds ratio 3.27). Continuous abstinence rates from weeks 4-52 continued to be more than double for Zyban™ compared to placebo (22% vs.9%, $p<0.001$, odds ratio 2.78). From Week 3 through Week 52 weekly point prevalence abstinence in the Zyban™ group was significantly higher compared to placebo (Week 52: 27% vs. 12%, $p<0.001$, odds ratio 2.87). Common adverse events for both treatment groups were insomnia, dry mouth, nausea and dizziness (incidence was greater in the Zyban™ arm) and headache (similar incidence in both treatment groups). Adverse Events leading to withdrawal were comparable between treatment groups (Zyban™ 5% vs. placebo 6%). Analysis of the blood pressure data did not show any statistically or clinically significant effect of treatment.

Conclusions: Our study is the first to show that after 7 weeks treatment with Zyban™, more than twice as many smokers with cardiovascular disease were abstinent at one year compared to placebo, and the safety profile of Zyban™ was similar to that seen in studies conducted in a general smoking population.

1 US Dept of Health and Human Services. The Health Benefits of Smoking Cessation: A Report of the Surgeon General. DHHS Publication No. (CDC) 90-8416; 285 - 296, 1990

THE VESSEL WALL AS A TARGET OF HYPERTENSION

1936 AT2-mediated and NO-dependent vasorelaxation by angiotensin II in SHR treated with losartan

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Vasoconstrictive and proliferative effects of Ang II are mediated by AT1 receptors. The effects of Ang II mediated via AT2 subtypes are less defined. However, growing evidence show that AT2 may be involved in cardiovascular responses to Ang II under certein conditions. The present study was designed to investigate the role of AT2 receptors on aortic vasoreactivity during chronic AT1 blockade with losartan in spontaneously hypertensive rats (SHR).

SHR and WKY (12-13 weeks old n=8) received losartan (30 mg/Kg/day) in the drinking water for 8 weeks. Untreated animals were also studied (n=8). Systolic blood pressure (BP) was measured before and at the end of the treatment by tail cuff method. Isometric tension was continuously recorded in isolated aortic rings. Nitric oxide (NO) release was detected by using the fluorescent probe diaminofluorescein (DAF-2).

BP was significantly reduced only in SHR treated with losartan ($p<0.05$). During submaximal contraction to norepinephrine (10-6 mol/L), Ang II (10^{-6}-10^{-4} mol/L) induced concentration-dependent relaxations only in aortas isolated from treated SHR and not in the untreated animals of both strains. These relaxations were inhibited by the selective AT2 receptor blocker PD123319 ($3x10^{-5}$ mol/L) as well as L-NAME ($3x10^{-5}$ mol/L) and B2 receptor antagonist Hoe-140 ($3x10^{-5}$ mol/L, n=6-8, $p<0.05$). Accordingly, NO production was significantly increased by Ang II only in SHR treated with losartan as assessed by DAF-2 (21±3 and 33±6 relative units for quiescent vs stimulated rings, respectively, n=3, $p<0.05$). By contrast, Ang II did not exert any stimulatory effect in untreated SHR (24±3 and 23±1 relative units for quiescent vs stimulated rings, respectively). Furthermore, DAF-2 fluorescence did not differ in quiescent and Ang II stimulated rings isolated from treated and untreated WKY (19±1 and 19±1 vs 25±3 and 28±1 relative units, respectively, n=3). In a separate group of SHR (n=5) acute exposure to losartan did not unmask any vasorelaxant effect of Ang II.

The present findings demonstrate for the first time an AT2 mediated vasorelaxation by Ang II in SHR chronically treated with losartan. Our results also suggest an involvement of the bradykinin-NO pathway in Ang II-induced vasorelaxation.

1937 Relaxin, a newly described cardiac hormone, is a potent, endothelium dependent, vasodilator in human resistance arteries

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Introduction: Though traditionally recognised as a hormone of parturition, relaxin has been shown to be secreted by the myocardium and production is increased in heart failure. We have compared the vasodilator action of relaxin to that of another cardiac secreted peptide, atrial natriuretic factor (ANF). We have also studied relaxin's mechanism of vasorelaxation.

Method: Small resistance arteries isolated from gluteal biopsies, taken from patients (n=8) with coronary heart disease (CHD) and normal left ventricular systolic function, were studied on a wire myograph. After start up protocols to ensure vessel viability and endothelial integrity, each set of vessels was preconstricted with norepinephrine. Cumulative concentration response curves (CCRCs) were constructed comparing relaxin with ANF. CCRCs were also constructed for relaxin comparing arteries whose endothelium had been removed by the established method of intraluminal rubbing with a human hair.

Results: The threshold concentration required to produce a 10% relaxation response was 3pM for relaxin compared with 10nM for ANF. Relaxin was therefore 1000 fold more potent than ANF. ($P<0.05$ using comparison of curves one way ANOVA for repeated measures). Both relaxin and ANF achieved similar maximal response at the highest concentration used.

A statistically significant difference ($P<0.05$) was found between arteries whose endothelium had been removed, where relaxin's vasodilator response was almost completely abolished, compared to the arteries with intact endothelium.

Conclusion: The newly described cardiac hormone relaxin is a more potent vasodilator than ANF in human resistance arteries and is endothelium dependent. It may, therefore, be important in regulating vascular tone and manipulation of relaxin secretion, metabolism and/or receptors may be of therapeutic interest in cardiovascular disease.

1938 Endothelial and contractile function of small resistance artery from hypertensive and diabetic patients: effects of insulin

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We have previously demonstrated that high-dose insulin may induce an increase of the sensitivity to norepinephrine (NE) in mesenteric small resistance arteries of spontaneously hypertensive rats.

Objective: To evaluate the effect of low and high dose insulin on the dose-response curve to NE and acetylcholine (ACH) in subcutaneous small resistance arteries of hypertensive and diabetic patients.

Methods: Ten patients with essential hypertension (EH), 7 patents with non insulin-dependent diabetes mellitus (NIDDM) and 8 patients with both EH and NIDDM (EH+NIDDM) were included in the study. Subcutaneous small resistance arteries (relaxed diameter 160-280 mm) were dissected and mounted on a micromyograph (Mulvany's technique). A concentration-response curve (CRC) to NE (cumulative concentrations from 10^{-8} to 10^{-5} mol/L) and to acetylcholine (cumulative concentrations from 10^{-9} to 10^{-5} mol/L) was performed in the presence or absence of insulin 715 pMol/L (low dose, ld) and 715 nMol/L (high dose, hd).

Results are summarized in the Table (*=$p<0.05$ vs. basal). A significant reduction in the contractile response to NE was observed in the three groups after pre-incubation of the vessels with high-dose insulin (ANOVA between CRC to NE: EH: p=0.02, NIDDM: p=0.03, EH+NIDDM: p= 0.004). No statistically significant effect of low-dose insulin was detected. No difference in the CRC to ACH before or after pre-contraction with either low or high dose insulin was observed in any group (ANOVA=NS in any case).

	EH (n=10)	NIDDM (n=7)	EH+NIDDM (n=8)
Basal NE 10^{-5} mol/L (kPa)	91±47	96±31	105±31
NE 10^{-5} mol/L + low-dose insulin (kPa)	101±36	92±44	103±49
NE 10^{-5} mol/L + high-dose insulin (kPa)	67±30*	80±42*	88±32*

Conclusions: Insulin at high doses seems to induce a decrease in the reactivity to NE in subcutaneous small resistance arteries of patients with NIDDM or EH. This effect does not seem to involve endothelium-dependent mechanisms.

1939 Statins improve endothelial dysfunction in normocholesterolemic mineralocorticoid hypertension

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Background: Statins reduce cardiovascular morbidity and mortality. These beneficial effects, however, cannot be fully explained by their lipid-lowering potential. As such, we investigated the impact of rosuvastatin on endothelial function, the key event in early atherogenesis, in an experimental model of normocholesterolemic hypertension.
Methods: To further evaluate statin-mediated vascular effects, hypertension was induced in Wistar-Kyoto rats by inhibition of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) which provides mineralocorticoid receptor specificity for aldosterone by metabolizing glucocorticoids to their receptor inactive 11-dehydro derivatives. Inhibition of 11β-HSD2 by liquorice-derived glycyrrhizic acid (GA) therefore results in sodium retention and hypertension. GA was added to the drinking water (3 g/L) for 21 days. From day 8 to 21 rosuvastatin (20 mg/kg/d) or placebo were added to chow. Endothelium-dependent and -independent function were assessed as response to acetylcholine (ACh, 10^{-10}-10^{-5} mol/L) and sodium nitroprusside (SNP, 10^{-10}-10^{-5} mol/L) in isolated aortic rings. In addition, vascular reactivity to endothelin-1 (ET-1; 10^{-10}-10^{-7} mol/L), norepinephrine (NE; 10^{-10}-10^{-5} mol/L) and potassium chloride (KCl, 100 mmol/L) were investigated.
Results: Blood pressure increased in 11β-HSD2 deficient rats treated with GA (175 vs. 153 mmHg in controls; $P<0.01$). Endothelium-dependent relaxations to acetylcholine (10^{-10}-10^{-5}) in aortic rings were blunted after GA treatment (p£0.005 vs. control) and completely blocked by NO-synthase inhibitor L-NAME, while responses to SNP remained unchanged. Rosuvastatin normalized NO-mediated endothelial function in hypertensive animals ($p<0.01$ vs placebo) although blood pressure and cholesterol levels were not affected by rosuvastatin treatment. In addition, vascular reactivity to norepinephine, but not to ET-1, was attenuated by rosuvastatin treatment ($p<0.05$ vs. control).
Conclusion: These data for the first time show that statins improve endothelial dysfunction in normocholesterolemic mineralocorticoid hypertension without affecting blood pressure and cholesterol levels.

1940 Inflammation induced hyporeactivity to vasoconstrictors can be reversed by antioxidants

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Background: Hyporeactivity to exogenously administered catecholamines is present in acute inflammation and sepsis. The underlying mechanisms in humans are not fully revealed, but oxidative stress may play a significant role. Further it is unclear, whether this hyporeactivity is also detectable for vasoconstrictors which do not act via adrenoceptors.
Methods: In randomized, double blind cross over studies, forearm blood flow responses to Noradrenaline (NE), Vasopressin (VP), and Angiotensin II (ATII) were assessed before and after induction of acute systemic inflammation by low doses of E. coli endotoxin (LPS, 2000 IU/kg iv) or after placebo administration in 9 healthy volunteers. The effect of intraarterial Vitamin C (24 mg/min) or placebo on NE induced vasoconstriction was studied in 8 additional subjects 4 hours after LPS, respectively.
Results: The systemic inflammatory response was associated with systemic vasodilation, increased white blood count, elevated body temperature and reduced Vitamin C plasma concentrations. LPS significantly decreased the responses of FBF to NE by 59%, to VP by 51% and to ATII by 25% ($p<0.05$, all effects). Vasoconstriction to ATII was reduced to a lesser extent by LPS than the other constrictors ($p<0.05$). Coadministration of Vitamin C completely reversed the reduced responsiveness to NE, which was comparable to that observed under baseline conditions.
Discussion: Reduced responsiveness to vasoconstrictors in acute inflammation is not limited to adrenoceptor agonists, but also present with other vasoconstrictors. Oxidative stress may play an important role in the pathogenesis of hyporeactivity to vasoconstrictors during acute inflammation and sepsis.

THE UPS AND DOWNS OF ENDOTHELIAL FUNCTION

1942 Inhibition of Akt-phosphorylation by thrombin, histamine and lysophosphatidylcholine in endothelial cells. Differential role of protein kinase C

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The serine/threonine protein kinase Akt is involved in embryonic vascular development and neoangiogenesis as well as in several endothelial cell functions, including activation of endothelial NO-synthase (eNOS) and promotion of endothelial cell survival. We have examined the effects of the G-protein activators thrombin and histamine as well as lysophosphatidylcholine (LPC), a mediator of vascular injury, inflammation and atherosclerosis, on Akt phosphorylation in cultured human umbilical vein endothelial cells (HUVEC). Akt phosphorylation was analyzed with the phosphospecific Akt (ser473) antibody by Western blotting. While epidermal growth factor (EGF) was a potent stimulator of Akt-phosphorylation histamine, thrombin and LPC blocked its activation when used in cotreatment with EGF. Following inhibition or downregulation of protein kinase C (PKC) the inhibitory effect of both histamine and thrombin on endothelial response to EGF was prevented. Furthermore, stimulation of PKC, using short term TPA treatment, markedly inhibited the stimulatory effects of EGF on Akt-phosphorylation. Conversely, while LPC also inhibited EGF mediated activation of Akt-phosphorylation, inhibition or downregulation of PKC did not prevent its inhibitory effect. Akt-phosphorylation was also increased by sphingosine-1-phosphate (S1P)treatment and this activity was influenced by the various cotreatments in the same way as the activation by EGF.
Overall, the present study demonstrated that the G-protein activators thrombin and histamine inhibited both EGF and S1P mediated Akt-phosphorylation in HUVEC by activation of PKC while the inhibitory effects of LPC were independent of PKC.

1943 Stretch-induced imbalance between endothelial nitric oxide and superoxide anion production: protective effects of quinaprilat and losartan

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Nitric oxide (NO) and superoxide (O2-) are free radicals produced by cells of the blood vessels, and their interaction may play an important role in the pathogenesis of vascular disease. Mechanical forces such as pulsatile stretch are involved in O2- production.
To clarify the effect of quinaprilat and losartan on the balance of these free radicals, human aortic endothelial cells (HAEC) were exposed to pulsatile stretch in the presence and the absence of these compounds. Rhytmic stretching was given for 60 minutes by a Flexercell strain unit. O2- production was measured as the superoxide dismutase-inhibitable reduction of cytochrome c. In situ measurements of NO were performed by porphyrinic microsensor. Angiotensin II levels in cultured medium were significantly increased by pulsatile stretch (0.3±0.01 and 0.42±0.03* ng/ml for control vs stretch, respectively, n=6,*$P<0.05$). Stretch-induced production of O2- was inhibited by quinaprilat [7.1±1 vs 2.8±0.7* and 3.9±0.9*, 3±0.7*,1.1±0.8* nmol/60min/105cells for stretch vs control and stretch plus quinaprilat (10-8-10-6M), respectively, n=3-7,*$P<0.05$ vs stretch]. Losartan significantly reduced stretch-induced O2-production only at the highest concentration [3.9±1.2, 4.6±0.5 and 1.8±0.2* nmol/60min/105cells for stretch plus losartan (10-8-10-6M), respectively, n=3-7, *$P<0.05$ vs stretch]. Accordingly, NO concentrations were decreased by stretch (163±9, 275±12* nmol/L for stretch and control, respectively, n=9, *$P<0.05$). Both quinaprilat and losartan prevented the stretch-induced inhibition of NO release [189±16, 231±14*, 313±32* nmol/L for stretch plus quinaprilat (10-8-10-6M) and 118±7, 165±14, 238±19* nmol/L for stretch plus losartan (10-8-10-6M), respectively, n=9, *$P<0.05$ vs stretch].The restoring effects of quinaprilat and losartan on NO release were abolished by bradykininin B2 (Hoe140) and AT2(PD123319) receptor antagonists [175±8 and 111±8 nmol/L for quinaprilat (10-6M) plus Hoe140 (10-7M) and losartan (10-6M) plus PD123319 (10-7M), respectively, n=9]. Interestingly enough, the effect of losartan was also abolished by Hoe140 (147±17 nmol/L).
These results suggest that modulation of renin angiotensin system at different levels may equally affect the balance between NO and O2- production. Quinaprilat improves endothelial function by inhibiting stretch-induced O2- production and restoring NO release by inhibition of bradykinin degradation. Furthermore, this study provides direct evidence that also losartan exerts similar effects via AT2-mediated B2 receptor activation.

1944 Long-term upregulation of eNOS expression and activity in endothelial cells by proteasome inhibition

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One of the most important post-transcriptional pathways in eukaryotic cells is the ubiquitin-dependent degradation of proteins by the 26S proteasome. Proteasome inhibtion (PI) reduces restenosis and neointima formation by antiproliferative, antiinflammatory and proapoptotic mechanisms. Since these effects may be also mediated by nitric oxide (NO), we investigated in the present study how PI affects endothelial NO synthase (eNOS) regulation in endothelial cells. Bovine pulmonary arterial endothelial cells (BAEC) and human umbilical vein endothelial cells (HUVECs) were treated with the proteasome inhibitor MG132 for 24 and 48h. Incubation of the cells with MG132 in ultra-low doses (50-500 nM) significantly increased mRNA (online PCR) and protein levels (western blot) of eNOS by 2 to 3fold in a dose-dependent manner. Comparable results were obtained with MG262, whereas ALLM, a non proteasomal cathepsin inhibitor was ineffetive, indicating specificity of the reaction. eNOS activity determined by conversion of L-[3H]arginine to L-[3H]citrulline in vitro and in vivo was also significantly enhanced after PI for 24 and 48 h. Interestingly, time course experiments revealed that incubation of endothelial cells with a single dose of MG132 (50 nM-250nM) was sufficient to significantly enhance eNOS protein and enzyme activity up to 7 days. Western blots evidenced accumulation of poly-ubiquitinylated proteins in the cells demonstrating efficiency of PI after incubation with these very low doses used in our study. Since alpha-amanitin, an inhibitor of RNA polymerase II, strongly reduced overall eNOS mRNA without influencing PI-induced elevation of eNOS mRNA level, protein content or activity, we assumed that PI enhances eNOS by enhancing mRNA stability. These findings suggest a major role of the ubiquitin-proteasome pathway in regulating eNOS protein turnover, thereby providing a novel mechanism to enhance nitric oxide activity.

1945 Statins prevent downregulation of human endothelial NO-synthase gene expression by thrombin: role of Rho/Rho-kinase and protein kinase C

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Thrombin generation and decrease in endothelial nitric oxide synthase (eNOS) gene expression play a pivotal role in acute ischemic cardiovascular events. HMG-CoA reductase inhibitors (statins) demonstrate great beneficial effects. We investigated the regulatory mechanisms of eNOS gene expression by thrombin and the protective role of HMG-CoA reductase inhibitors in cultured endothelial cells isolated from human umbilical veins. Stimulation of the cells with thrombin (4U/ml) for 24 hours down-regulated eNOS protein level (57% decrease). This effect of thrombin was prevented by the HMG-CoA reductase inhibitors simvastatin (10 μM) and cerivastatin (1 μM), and also abrogated by protein kinase C (PKC) inhibitor calphostin C (0.3 μM) or depletion of PKC (i.e. exposure of the cells to 0.1 μM of phorbol ester for 24 hours). Thrombin (4U/ml) activated RhoA (measured by pull-down assay) and Rho-kinase (measured by phosphorylation of the substrate MYPT-1) that was inhibited by simvastatin (10 μM). Calphostin C (0.3 μM), had no significant effect on RhoA, but inhibited Rho-kinase activation in response to thrombin. Similar to thrombin, adenoviral overexpression of a constitutively active RhoA (Rho63) or Rho-kinase (CAT) suppressed eNOS expression. The inhibition of eNOS gene expression by Rho63, but not CAT was abolished by PKC depletion. Thus, long-term stimulation of endothelial cells with thrombin leads to down-regulation of eNOS gene expression via activation of a sequential signalling cascade namely RhoA/PKC/Rho-kinase. Statins protect against endothelial dysfunction induced by thrombin via inhibition of RhoA, which may importantly contribute to the benefits of the drugs in prevention of ischemic cardiovascular events such as ischemic stroke or acute coronary syndromes.

1946 Increased endothelial tetrahydrobiopterin levels in GTPCH-transgenic mice

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Background There is reduced NO bioavailability in vascular disease states due to eNOS dysfunction. Tetrahydrobiopterin (BH4) is a required co-factor for NO production by eNOS. Supplementation of high dose BH4 improves endothelial dysfunction in humans and animals, but it is unclear whether intracellular BH4 levels are limiting in vascular disease. To investigate the role of BH4 in modulating eNOS function in vivo, we aimed to create transgenic mice with increased endothelial BH4 levels, by targeted over-expression of the rate-limiting enzyme in BH4 biosynthesis, GTP cyclohydrolase-1 (GTPCH).
Methods Transgenic mice were generated in a C57Bl6 background using a construct comprising human GTPCH cDNA, and the endothelial-specific mouse Tie-2 promoter. Founders were identified by genomic PCR, Southern blotting and FISH. Mouse organs were harvested at 6-8 weeks. BH4 levels in tissues and cells were measured with differential iodine oxidation and HPLC.
Results Several GTPCH-transgenic mouse lines were generated. One line had transgenic GTPCH expression by RT-PCR. BH4 levels in heterozygote transgenic heart, lung and aorta, were higher than in controls, but there was no difference in liver or plasma (table), and BH4 levels in transgenic endothelial cells were higher than in myocytes.

BH4 levels in heterozygote GTPCH-transgenic and wild-type mouse organs

Organ (n=3 per group)	BH4 levels (mean (SEM)) (pmol/mg protein)		P value (ANOVA)
	GTPCH-transgenic	Control	
Heart	7.6 (2.6)	0.5 (0.1)	0.06
Lung	25.7 (4.8)	9.2 (2.8)	0.03
Aorta	2.4 (0.6)	1.2 (0.7)	0.04
Liver	43.8 (20)	27.6 (6.5)	0.48
Plasma	7.3 (4.4)	5.2 (2.1)	0.69

Conclusions Targeted endothelial-specific GTPCH over-expression in transgenic mice results in increased endothelial BH4 levels. This is a promising in vivo model to investigate modulation of eNOS dysfunction by intracellular BH4 in vascular disease.Table

1947 ESR measurement of vascular xanthine-oxidase and NAD(P)H-oxidase activity in patients with coronary artery disease

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Increased vascular superoxide anion (O2-.) formation leads to inactivation of nitric oxide thereby contributing to impaired flow dependent endothelium-mediated vasodilation (FDD) in patients with coronary artery disease (CAD). However, the enzymatic sources of O2-. in human arteries are poorly characterized. We examined xanthine oxidase (XO) and NAD(P)H-oxidase activities in atherosclerotic (AS) and non-atherosclerotic (non-AS) coronary arteries by electron spin resonance spectroscopy (ESR) using the spin trap 1-hydroxy-3-carboxy-pyrrolidine (CPH). In AS arteries, XO and NAD(P)H oxidase activities were 13 ± 2 and 12 ± 2 nmol O2-. x μg-1 x min-1, respectively, i.e. significantly higher as compared to non-AS coronary arteries (7 ± 1.5 and 9.5 ±0.9 nmol O2-. x μg-1 x min-1,respectively; $P < 0.05$ for both compared to AS vessels). Furthermore, we examined endothelium-bound XO activity (released into plasma by heparin bolus injection) in 21 patients with CAD and 10 controls using ESR. FDD of the radial artery was determined in these subjects before and after infusion of the antioxidant vitamin C (25 mg x min-1, i.a.). Endothelium-bound XO activity was increased in patients with CAD (25 ± 4 vs 9 ± 1 nmol O2-.x μl-1 x min-1;$P < 0.01$), correlated inversely with FDD (r=-0.55; $P < 0.05$), and was positively related to the effect of vitamin C on FDD (r=0.54; $P < 0.05$).
Conclusion: These studies represent the first ESR measurements of xanthine oxidase and NAD(P)H oxidase in human vessels and strongly support the concept that increased activities of both enzymes contribute to increased vascular oxidant stress in patients with coronary artery disease. The inverse correlation of XO activity and endothelium-mediated vasodilation supports the concept that increased XO activity contributes to endothelial dysfunction in vivo and may thereby promote the atherosclerotic process.

LONG-TERM RESULTS OF VALUE SURGERY

1948 Doppler echocardiographic comparison of standard versus the haemodynamic-plus St Jude Medical Valve in aortic position: a population-based study

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Background: The Hemodynamic-Plus St Jude valve (HP) is a new type of mechanical prosthesis that has, in vitro, larger effective orifice area (EOA) than the standard SJ (SSJ) (1.63 & 2.06 cm^2 for 19 SSJ & 19 HP & 2.06 & 2.55 cm^2 for 21 SSJ & 21 HP respectively). However, it is unknown whether the better in vitro hemodynamics translate to better in vivo performance, & to a lower incidence of prosthesis-patient mismatch (PPM) (defined as EOA indexed to body surface area (BSA) <0.85 cm^2/m^2), both of which may affect long-term outcome.
Methods & Results: Between 1985 & 2000 at Mayo Clinic, 518 pt had aortic valve replacement using 19 or 21 mm St Jude prostheses. A first postoperative transthoracic echocardiography was performed within 134 days after surgery in 446 (86%) pt. EOA was calculated using the continuity method in 433 (84%) pt, & the mean gradient was measured using the simplified Bernoulli equation, in 438 (85%) pt. The table compares demographic & echo data of 19 SSJ to 19 HP & 21 SSJ to 21HP respectively.

	19 mm (n=183)		P	21mm (n=335)		P
	S-SJ	SJ-HP		S-SJ	SJ-HP	
H	66	117		184	151	
Sex (Female) %	94	88	0.3	66	45	0.0001
Age (years)	63±16	66±13	0.4	63±11	61±14	0.9
Ejection Fraction %	60±12	58±15	0.6	57±13	58±11	0.8
BSA (m^2)	1.62±0.2	1.7±0.2	0.004	1.79±0.2	1.86±0.2	0.0002
Mean gradient (mm Hg)	20±9	18±9	0.01	19±7	17±7	0.001
EOA (cm^2)	1.12±0.2	1.28±0.3	0.002	1.4±0.4	1.62±0.4	0.0001
EOA/BSA (cm^2/m^2)	0.7±0.16	0.76±0.2	0.09	0.8±0.25	0.89±0.24	0.0002
PPM (%)	86	70	0.04	66	46	0.001
7 years survival (%)	65±6%	48±8%	0.3	72±4%	56±9%	0.5

Conclusion: SJ-HP has, in vivo, significantly lower mean gradient & larger EOA than SSJ in both 19 & 21 mm sizes. Morever, the % of PPM is higher in pt with SSJ for both sizes. At 7 years, the hemodynamic advantage of SJ-HP does not appear to be associated with improved survival. Longer follow up may be necessary to determine whether the in vivo hemodynamic advantage of SJ-HP translates into improved survival.

1949 Clinical outcome after implantation of the Prima Edwards Stentless Bioprosthesis model 2500: a multicenter study

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Purpose: This study was performed to collect prospective safety and effectiveness data of the Edwards Prima Stentless Bioprosthesis in patients requiring replacement of a native aortic heart valve.
Methods: Between 1991 and 1993 four centers implanted the Prima Stentless Bioprosthesis in 160 patients with the subcoronary technique using a common, prospective protocol. Patients were followed for both acute and long-term evaluation of complications, NYHA class improvement and hemodynamic measures. The mean age at implant was 70.6 ± 6.1 years, with 53.8% of the patients being male. The maximum follow-up was 8.2 years with a mean of 5.8 ± 2.1 years. The cumulative total data collected represents 934.4 patient-years.
Results: At the 1 and 4-5 year post implant interval, 93.8% and 75.0% of the patients, respectively, showed improvement in their last available NYHA classification versus the preoperative NYHA classification. The table shows the principal safety parameters. Rate of thromboembolism, thrombosis, AC-related hemorrhage, paravalvular leak and incidence of endocarditis through eight years post implant showed acceptable results as compared to the FDA OPCs for tissue valves. The effectiveness of the device was demonstrated by low mean gradients (15.9±1.1 mmHg fore size 21, 9.9±1.6 mmHg fore size 23, 8.8±1.9 mmHg fore size 25, 6.5±2.1 mmHg fore size 27 and 4.2±2.6 mmHg fore size 29) at 4-5 years follow up and absence of regurgitation.

Valve-related complications	Operative (%)	Postoperative (%/Pt-Yr)	Freedom from events (%)
expiration (all)	3.8	5.5	66.6 ± 19.2
valve related expiration	1.3	2.7	86.1 ± 16.1
valve related reoperation/explant	0.0	1.1	95.4 ± 10.2
structural valve deterioration	0.0	1.8	87.2 ± 15.6
hemolysis	0.0	0.2	100.0 ± 0.0

Conclusions: The Edwards Prima Stentless Bioprosthesis is safe and effective as an aortic valve replacement in the subcoronary configuration as evidenced by low rate of valve-related complications, the improvement in NYHA classification and the acceptable results of hemodynamic evaluation at one and five years post implant.

1950 Up to 8 years experience with the Ross procedure using the subcoronary and inclusion technique

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Purpose Since the early 90's the pulmonary autograft is predominantly implanted as a full root replacement for less regurgitation is expected in the long term. However, there is a certain risk of dilation of the root over time bearing the potential to influence valve function. We favored since 8 years the original subcoronary and inclusion technique to preserve the root of the patient. Hemodynamic follow-up of the autograft implanted in this techniques is not well defined.
Methods Between 2/90 and 01/02 the Ross procedure was performed in 244 patients. The subcoronary and inclusion technique was performed in 231 patients (177 m/ 54 f), mean age 46.5±13.4 (15-70 years). The underlying aortic valve disease was an aortic insufficiency (AI) in n=75, stenosis in n=47, combined aortic valve disease in n=104 and an acute endocarditis in n=19 patients. Previous aortic valve surgery was performed in n=22. Last follow-up investigations including echocardiographic determinations of hemodynamic variables, autograft and homograft function were applied at a mean follow-up of 29.5±24.8 (0.1-84.5) months (543.7 patient years).
Results The hospital (n=2) and late mortality (n=2, non cardiac cause of death) were low. 2 patients were lost to follow-up. Late neurological events occurred in 4 patients. Reoperations n=5 (due to autograft insufficiency n=1, homograft stenosis n=2, homograft insufficiency n=1, auto- and homograft insufficiency n=1).
Autograft function was good (AI<=I°) in 96.3%, and acceptable (AI II°) in 3.7%. The maximum/ mean pressure gradient was 6.5±3.3 (2.1-25.9)/ 3.5±1.7 (1.2-13.2) mmHg. Homograft insufficiency was <=I° in 95.4%, II° in 4.1%, III° in 0.5%. Maximum and mean pressure gradients: 11.9±7.0 (2.2-42.6) and 6.2±3.7 (1.2-21.0) mmHg, respectively. Cardiac output was 5.4±1.7 l/min and ejection fraction 60±9.0%. Most patients were in NYHA class I (90.4%).
Conclusions Aortic valve replacement with a pulmonary autograft shows excellent hemodynamics with a low incidence of autograft failure or homograft obstruction at least in a short term period in the subcoronary or inclusion technique.

1951 Bicuspid valve preservation and concomitant repair of the ascending aorta and/or root

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Purpose: The surgical strategy for treatment of the aortic root and valve in aneurysmal or dissecting disease of the ascending aorta involving the aortic root is controversial. A congenital malformed aortic valve may lead in most circumstances to a valve replacement even if the leaflets itself are unremarkable. We reviewed our experience with bileaflet valve preservation in aortic surgery.
Method: Between October 1993 and November 2001 we operated upon 59 patients with a bicuspid aortic valve who had either a combined aortic valve dysfunction and ascending aortic pathology (aneurysm: n=42, type A dissection: n=9) or an ascending aortic pathology alone (n=8). Among these were 14 patients (23.7%) in which the aortic valve could be preserved during replacement of the ascending aorta and the aortic root (n=11) or the supracommissural ascending aorta (n=3). The age was 44.9±18.0 years. All these patients had an aneurysm (diameter 6.3±1.2, range 4.4-10 cm), one patient presented with acute aortic dissection type A. The aortic valve was insufficient in 7 patients (grade 1: n=1, grade 2: n=4, grade 3: n=2) and mild stenotic (grade 1) in one patient. Only leaflets without calcification and with dense tissue for secure suture fixation were regarded appropriate for repair independent of root pathology. Predominantly plication of the prolapsing leaflet with the raphe was performed. In one patient plication of both leaflets was feasible.
We followed the patients clinically and echocardiographically for 27.5±27.7 month (range 0.2-92.8 month).
Results: No patient required reoperation. No hospital or late death occurred. Two patients presented dyspnoea according NYHA grade 2, the others were asymptomatic without limitations in life. None of the patients reported thromboembolic events. No patient had an aortic valve insufficiency higher than grade 1. Other echocardiographic examination data were: mean aortic valve pressure gradient 5.1±2.6 mmHg, ejection fraction 67.2±8.0%, cardiac output 5.4±1.6 l.
Conclusion: The midterm results (up to 8 years) of aortic valve preservation during surgery on the ascending aorta and aortic root are encouraging provided careful selection of patients and techniques are thoroughly performed including concomitant repair of the aortic root.

1952 Five years experience with mitral valve homografts

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Introduction: We present our five years experience utilizing mitral HG's in mitral valve surgery. Patients and methods: 14 patients (mean age 46 ± 8 ys, 27-65 ys) had mitral HG's implanted. In 13 cases, the grafts were implanted in mitral position, once the septal leaflet of the tricuspid valve was replaced. The indications were mitral (n=6) or tricuspid endocarditis (n=1), mitral valve stenosis (n=3) and combined mitral valve disease (n=4). Complete mitral HG's were implanted in patients with combined mitral valve disease (n=4), mitral valve stenosis (n=3), and mitral valve endocarditis (n=1). Partial HG's were implanted in mitral (n=5) or tricuspid valve endocarditis (n=1). Preoperatively, the dimensions of the mitral valve were measured using transesophageal echocardiography (TEE). Surgery started with papillary muscle implantation with a side-to-side anastomosis to the recipients papillary muscle, followed by the annulus. For annular stabilization, a Carpentier ring was implanted. Follow-up was initiated six months postoperatively and then continued on a yearly basis, inlcuding clinical examination, ECG, and echocardiography. The following parameters were determined echocardiographically: left atrial size, left ventricular enddiastolic and endsystolic diameter, pressure gradient across the mitral valve (C/W-Doppler,Bernoulli-equiation), and mitral regurgitation. Results: All patients survived the operation. Intraoperative TEE revealed an insufficiency °I in 7 patients. Follow-up is complete in all patients (mean period of 30 months,6-66 m.). Two patients had repeat valve replacement due to newly aquired endocarditis. One more patient had to be reoperated due to chordal rupture one year postoperatively. In the remaining 11 patients, the morphological and functional state of the implanted HG's remained unchanged during follow-up. The freedom of valve-related events was 93% after one year and 75% after two years respectively. At six month follow-up, ECG and echocardiography revealed sinus rhythm and sufficient atrial contractions in all cases, so anticoagulation was discontinued in all patients. At the last follow-up, the pressure gradients were 3.4 ± 0.6 mmHg for complete HG's and 2.8 ± 0.6 mmHg for partial HG's. Conclusions: Mitral HG's can be used with acceptable mid-term results in selected cases with good left ventricular function and only slighty dilated left ventricles. Especially partial mitral HG's represent an additional technique for mitral valve repair. Their obvious sensibility to bacterial infections makes strict endocarditis-prophylaxis mandatory.

1953 Importance of the etiology in the outcomes of mitral valve repair: an 8-year follow-up

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Background: Mitral regurgitation prognosis should be made on the basis of the valve dysfunction etiology. This study analyzes 8-year outcomes of mitral valve repair (MVR) and assesses the significance of association between the etiology of mitral insufficiency and MVR outcomes.
Methods: From September 1992 through June 2001, 302 patients underwent MVR. Mean age was 58±14 years (range 21-82 years); 195 patients (65%) were men. The etiology was: myxomatous (Mx) in 187 patients (64%); ischemic (Is) in 62 patients (17%); rheumatic (Rh) in 18 patients (6%); secondary dilated cardiomyopathy in 11 patients (3.5%); infectious endocarditis in 13 patients (4.5%), and secondary aortic valve disease with ventricular dysfunction in 11 patients (3.5%). Freedom from events was studied by Kaplan Meier curves (confidence interval 95%): survival, reoperation, endocarditis, and thromboembolism. Mx etiology was compared to the rest of the etiologies using log rank test.
Results: Mean follow-up was 44±50 months.

	Hospital Mortality	Survival	Reoperation	Infectious Endocarditis	Thromboembolism
Total	6.3% (19/302)	89% (85-93%)	95% (92-97%)	98% (93-100%)	98% (93-100%)
Mx	3.8% (7/187)	91% (87-95%)	95% (91-98%)	99% (94-100%)	99% (94-100%)
Is	13% (8/62)	56% (45-67%)	98% (93-100%)	100%	99% (94-100%)
Rh	0% (0/18)	94% (84-100%)	83% (67-100%)	98% (93-100%)	96% (90-100%)
Dilated Cardio-myopathy	9% (1/11)	78% (61-100%)	100%	100%	
Infectious Endocarditis	7.6% (1/13)	90% (86-94%)	90% (86-94%)	100%	100%

Survival was significantly lower in patients with Is than in patients with Mx (p=0.03 and p=0.04). Rh showed a tendency for reoperation (p=0.05).
Conclusion: Patients with Mx undergoing MVR have better outcomes than those with Is and Rh. Thus, the results of MVR will clearly depend on the etiology of mitral insufficiency.

CARDIOVASCULAR DISEASES IN THE YOUNG: CONSEQUENCES LATER ON

1954 Effects of serum cholesterol levels on inflammatory markers and haemostatic/thrombotic mechanisms in children with familial hypercholesterolemia

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Background: It is well known that children with familial hypercholesterolemia (FH) are likely to establish premature coronary atherosclerosis. Furthermore it has been established that inflammatory process is an important component in the pathophysiology of endothelium and atherosclerosis. Proinflammatory markers such as vascular cell adhesion molecule-1 (sVCAM-1) and intercellular adhesion molecule-1(sICAM-1) have been proposed as new risk factors for cardiovascular disease. Apart from inflammation, haemostatic factors seem to play a pivotal role in the atherosclerotic process and several factors such as plasma levels of factor VII(fVII), von Willebrand factor (vWf) and fibrinogen are related to premature atherosclerosis and are affected in endothelial dysfunction. The purpose of our study was to investigate the impact of cholesterol levels on inflammatory, thrombotic and haemostatic markers in children with familial hypercholesterolemia.
Methods: We studied 21 children (aged 10-20) with FH and 17 controls of the same age. Serum levels of TNF-a, sICAM-1 and sVCAM-1 as well as plasma levels of fVII, VWF and fibrinogen were determined using enzyme linked immunosorbent assay (ELISA). Pearson's correlation was determined between total cholesterol and inflammatory and thrombotic/ fibrinolytic components.
Results: Serum cholesterol level was 316.4±16 mg/dl and 155±4.5mg/dl in FH group and in controls respectively. Serum level of cholesterol was correlated to fibrinogen plasma levels (r=0.4, p<0.04), to vWF levels (r=0.51, p<0.05), to VCAM-1 levels (r=0.62, p<0.62) and to ICAM-1 serum levels (r=0.66, p<0.05). No significant correlation was found between cholesterol and TNF-a and factor VII.
Conclusions: In children with familial hypercholesterolemia a significant correlation was found between serum cholesterol levels and inflammatory and thrombotic/haemostatic markers. These findings indicate that the increased inflammation and the thrombotic process observed in these children with high serum cholesterol may play an important role in the development of premature atherosclerosis.

1955 Relations of localization, heamodynamic changes and thrombus formation in coronary aneurysms having history with Kawasaki disease

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Thrombus formation in coronary aneurysms (AN) is an important complication of Kawasaki disease (KD), which often occurs giant aneurysms and can cause myocardial ischemia and infarction. We hypothesized that ANs could exist at the coronary artery branching sites because of reduced shear stress, and reduced shear stress inside AN also could relate the mechanism of thrombus formation strongly. 111 children aged 2 to 16 years old who had left coronary abnormality by 2-D echo and were 1 to 15 years from the onset of KD were subjected. Patients had no significant stenosis in proximal and distal portion of AN and were divided into three groups by the maximum diameter of AN; giant aneurysms group (Group G: maximum diameter is more than 8mm, n=28), aneurysms group (Group A: maximum diameter < 8mm, n=44), and control group (Group N: normal-looking vessels by CAG, n=39). All patients had Aspirin and/or Warfarin. The averaged peak coronary flow velocity (APV) was measured in the middle of ANs in Group A and G, and branching sites of segment 5-6-11 in Group N using 0.0014-in Doppler flow guide wire (Cardiometrics), and shear stress were calculated by the simplified formula as: shear stress = 4mxAPV/(R/2), where m is blood viscosity measured by viscocimeter, R is maximum inner diameter of aneurysm or coronary vessel measured by CAG or IVUS. Also, IVUS were performed for detection of thrombus and measurement of coronary diameters. Localization of ANs were detected by CAG and IVUS.
Results: The values of APV and shear stress in Group G (2.3±0.7, 11.8±3.6) were significantly low as compared to those in Group A (17.6±4.2, 22.6±2.4) and N (9.9±1.8, 11.8±3.6). Also, there were significant differences in the values of APV and shear stress between Group A and N. Thrombus formations were detected 85.7% only in Group G. Moreover, localization of ANs were observed 88.6% at branching position and 11.4% at non-branchig position in Group A, and 100% at branching position in Group G.
Conclusions: Coronary aneurysms localized at the coronary artery branching position predominantly because of reduced shear stress. Stagnation of coronary flow and reduced shear stress may critical play a role of giant aneurysm and thrombus formation intra coronary aneurysms in children with Kawasaki disease.

1956 Echocardiographic characterization of thoracic aorta dimensions in patients with Turner Syndrome

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Pts with Turner Syndrome (TS) are frequently affected by aortic disease which may progress into dissection and may be the cause of excessive mortality.The aim of this study was to assess, with 2D-echocardiography (2DE), aortic diameters (aortic root, AoR; supraaortic ridge, SAoR; ascending thoracic aorta, ATAo; aortic arch,AoRC; descending thoracic aorta,DTAo; abdominal aorta,ABAo) and to investigate the clinical characteristics associated with aortic pathology in an unselected group of 67 karyotypically proven TS pts (mean age 22±9 yrs). The Aortic Root Ratio (AoRR)(expected/observed aortic root diameter, according to a formula that incorporates age and BSA), was calculated in every case (AoRR=1=normal). According to centile distribution of AoRR, the population was divided into 3 groups, G1: <25th centile, n=18 (27%), mean AoRR 0.93±0.04(range 0.83-0.98); G2: 25th-75th centile, n=32 (48%), mean AoRR 1.06±0.05(range 1-1.16); G3: >75th centile n=17 (25%), mean AoRR 1.31±0.09 (range 1.19-1.47). No significant differences were observed between groups considering karyotype distribution, age at observation, weight at birth, BSA, systolic blood pressure, presence of thickening of the nucal fold, hormonal therapy (growth, estrogen, thyroid),cardiac dimensions, left ventricular wall thickness, cardiac function. Body Mass Index (kg/m^2) was significantly higher in G1 compared to G2 and G3 (53±12 vs 21±4.5 and 2±4.3, $p<0.05$),whereas congenital lymphedema occurred more frequently in G3 compared to G2 and G1 (yes vs no: 39% vs 18% in G3, 52% vs 46% in G2 and 9% vs 36% in G1, $p<0.05$). Not only AoRR diameter was significantly higher in G3 compared to G2 and G1 ($p<0.0001$), but aortic dilation showed to significantly extend toward the aortic arch in G3 compared to G2 and G1: SAoR 22±6 vs 19±4 and 16.5±3 mm,$p<0.05$; ATAo 26±5 vs 22±4 and 20±2.5 mm,$p<.0005$; AoRC 23±6 vs 19±3.6 and 20±3 mm,$p<.005$, but not to the DTAo 14±3.9 vs 14±3.4 and 14±2.2 mm or to the ABAo 13.2±2.1 vs 12.7±2.4 and 12.4±1.5 mm, p=ns. **Conclusions:** 1) pts with TS may present with proximal aortic diameters that are frequently below (27% with AoRR<1) or above (25% with AoRR>1.1) the normal expected values; 2) small AoR are associated with a higher BMI, that means small stature and/or overweight; 3) dilated aortas are more common in pts with congenital lymphedema suggesting a linkage with a connective tissue disorder; 4) when the AoR is involved, dilation of the SAoR, ATAo and AoRC is usually the case, thus explaining the association between TS and type A dissecting aortic aneurysm.

1957 Changes in regional right and left ventricular systolic function in tetralogy of Fallot: an ultrasonic strain and strain rate imaging study

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Background: The quantification of regional myocardial function in Tetralogy of Fallot (TOF) by conventional echocardiography may be difficult because of the complex morphology of the right ventricle (RV) and the associated altered geometry of the left ventricle (LV). Ultrasound-based peak systolic strain (S) (%) and strain rate (SR) (unit S^{-1}) are new parameters for quantifying regional deformation. For normal myocardium, the first is altered by changes in end diastolic volume/stroke volume, while the second correlates with local Dp/Dt.
Methods: A Doppler Myocardial Imaging study (DMI) was performed in 54 TOF patients (mean age 11±3yrs) who had undergone surgical correction. Of these 44 pts had moderate/severe pulmonary regurgitation. None had significant pulmonary stenosis. All patients were asymptomatic. Data were compared with those of 30 age matched controls (12±4yrs). Longitudinal systolic strain was measured for basal, mid and apical segments of the LV lateral and septal walls and from the RV free wall.
Results: Long axis S in each RV segment was significantly ($p<0.0001$) lower in TOF (S: Basal -18±6, Mid -21±5, Apical -21±6) than in controls (S: Basal -36±11, Mid -45±13, Apical -34±11). Moreover, regional S in TOF was significantly reduced in each segment of LV lateral wall and septum compared to controls ($p<0.02$). In TOF, regional SR was significantly lower in all RV and LV segments compared to controls (table). Radial LV function was also significantly ($p<0.001$) reduced in TOF (SR: 3.0±0.9; S: 45±17; Controls: SR: 3.7±1.1; S: 58±12). RVEDD correlated significantly with S ($p<0.0001$,R=0.67), but not with SR.
Conclusions: SR and S provide complementary information and showed reduced regional deformation properties in both ventricles for both long axis and radial function in asymptomatic TOF. SR measurements would appear to be a new volume independent parameter of regional RV and LV contractility which may improve the understanding of functional changes in these complex pts.

	TOF Septum	Controls Septum	TOF LV Lateral	Controls LV Lateral	TOF RV	Controls RV
Base	-1.5±0.4*	-1.8±0.6	-1.2±0.7*	-2.2±1.1	-1.4±0.7*	-2.4±0.6
Mid	-1.4±0.3*	-1.9±0.6	-1.6±0.6**	-2.1±1.0	-1.6±0.6*	-2.8±0.7
Apical	-1.3±0.4*	-1.7±0.3	-1.5±0.8***	-1.9±0.7	-1.5±0.5*	-2.5±0.6

*$p<0.0001$; **p=0.005;***p=0.02.

1958 Superior quantification of pulmonary blood flow by MRI compared to lung perfusion scintigraphy in patients with Fontan circulation

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Background: Quantitative evaluation of pulmonary perfusion using lung perfusion scintigraphy in patients with atriopulmonary anastomosis (APA) or cavopulmonary connections (TCPC, PCPC) is difficult due to preferential draining of the venae cavae to one lung. Scintigraphy is the gold standard and phase-velocity magnetic resonance imaging (PV-MRI) in combination with flow analysis software (Massflow ®) is a new technique in determing pulmonary perfusion. The aim of this study was therefore to compare these two methods for quantitative evaluation of pulmonary perfusion ratios in patients with APA, TCPC, or PCPC.
Methods and Results: We studied 15 patients with APA, TCPC, or PCPC (16 ± 7 years old, four female). Twelve patients (15 ± 8 years old, three female) with a single pulmonary blood source supplied by a subpulmonary ventricle, ensuring complete mixing of the radioactive tracer before entering the pulmonary circulation, served as control. Pulmonary scintigraphy and PV-MRI were performed in all patients. Bland-Altman analysis showed a clinically unacceptable difference of 7.1% right pulmonary blood flow (27.2% upper and -13.0% lower limit of agreement) between the two methods in the study group. The two methods agreed excellently in the control group (difference: -1.6%, 4.0% upper and -7.2% lower limit of agreement), showing that the bad agreement in the study group was caused by the problems encountered using pulmonary scintigraphy in patients with APA, TCPC, or PCPC.
Conclusions: Flow quantification with PVC MRI is feasible in patients after Fontan like palliation. Due to preferential caval flow into either lung side in patients with Fontan like circulation PV-MRI is more accurate in evaluation of pulmonary perfusion ratios than lung perfusion scintigraphy. It does not need two injections on subsequent days into the upper and lower limb, respectively. Another benefit of MRI may lie in the possibility of quantifiing and showing the cause of pulmonary blood flow patterns in one session. Neither scintigraphy nor angiography can meet both demands in one examination.

1959 Haemodynamic status and right ventricular performance in infants with hypoplastic left heart syndrome after modified Norwood operation

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Objective: To stabilise the systemic circulation and to prevent circulatory collapse in infants with hypoplastic left heart syndrome (HLHS) after the classic Norwood operation, there has been recently reintroduced the modification of first stage of palliation by placement a right ventricle – to – pulmonary artery shunt (RV – PA). To assess the influence of RV – PA on right ventricular function and hemodynamic changes after this modification, early (1 to 5 mo) postoperative echocardiographic (ECHO) results were compared with the preoperative parameters.
Material: Since June 2001 to January 2002, 18 consecutive infants (13 M, 5 F), at the mean age of 17 days (3 – 41), weighing 2.3 to 4.3 kg with HLHS, underwent modified Norwood operation with PTFE grafts placed between RVOT and the confluence of PA using 5 mm in diameter grafts in 17 pts and 4 mm in 1 pt. Two infants (11.1%) died early postoperatively. The survivors (16 pts.) comprised the study material.
Methods: Based on ECHO studies a comparative statistic pre- and postoperative analysis was made of RV end-diastolic and systolic volume (EDV, ESV) by Levine method, pulmonary (Qp), systemic (Qs) and combined (Qp+Qs) blood flow indexed for BSA, Qp/Qs, RV ejection fraction (EF), Tei index (TI), RV anterior wall thickening fraction (AWTF), heart rate (HR) and systemic blood saturation (SO2) assessed by pulse oximetry.
Results: A significant post- vs preoperative decrease of mean values was noted in SO2 (78.2 vs 87.5%, p=0.001), HR (124 vs 146/min, p=0.009), Qp+Qs (7.8 vs 10.6 l/min/m^2, p=0.004), Qp (2.7 vs 8.1 l/min/m^2, $p<0.001$) and Qp/Qs (0.6 vs 3.7, $p<0.001$). The values of Qs (4.8 vs 2.4 l/min/m^2, p=0.001), TI (0.53 vs 0.38, p=0.04) and BSA (0.25 vs 0.21, p=0.003) were significantly increased, while mean values of EDV (75.7 vs 80.9 ml/m^2), ESV (43.8 vs 44.9 ml/m^2), EF (41.9 vs 44.1%) and AWTF (38.2 vs 55.2%) remained statistically unchanged.
Conclusions: 1. Modified Norwood operation influences on significant postoperative reduction of the combined right ventricular output, pulmonary blood flow, Qp/Qs and consequently systemic blood saturation, and normalises the systemic blood flow in infants with HLHS. 2. This modification does not affect the right ventricular anterior wall contractility and systolic function but may deteriorate their global function in early postoperative period.

CHARACTERIZATION OF THE VULNERABLE PLAQUE BY HEAT, ELASTICITY OR MORPHOLOGY

1960 Safety of the "contact with the wall" coronary thermography methods. Comparison with standard catheters

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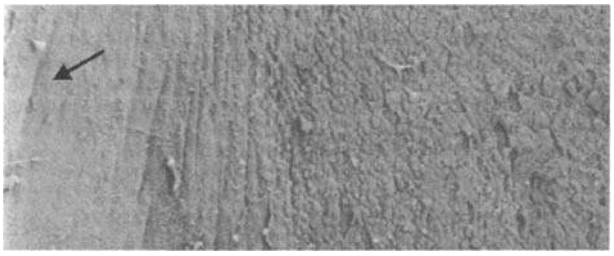
Background: Sensor-based thermography is being curently used to study the arterial wall temperature. Sensors include thermistors and thermocouples. In order for these sensors to give a measurement, good thermal contact with the arterial wall has to be established. The purpose of this study was to examine the safety of such a "thermal contact" and evaluate the impact on the arterial wall.
Methods: We used a thermography catheter with 4 thermistor sensors. When the catheter is in measuring configuration, the sensors come in close contact with the arterial wall and a motorized pullback is engaged.We studied the proximal left anterior descending artery in 15 non-atherosclerotic pigs. Pigs were separated in 3 equal groups: In group A we performed a single thermographic scan for a total length of 40mm, using a pullback speed of 0,3mm/sec. In group B we performed a single pullback (same length and speed) of a balloon catheter without inflating it. In group C we performed the same, but this time using a stent catheter. Animals were sacrificed immediately, and histology and electron microscopy (SEM) were performed.
Results: SEM showed clearly that in the case of thermography the sensors caused minor denudation of the endothelium that was strictly limited to the sensor contact area, while the basic membrane was left unharmed. In the case of the not-inflated balloon catheter there was also endothelial denudation with unharmed basic membrane; denudation was worse in the case of the not-inflated stent catheter.



Stent-catheter passage:denudation (arrow).

Conclusions: From this study, it is clear that in reality there is no such thing as non-contact catheter. Every intracoronary catheter has an impact on the endothelium and its function. However, when these devices are carefully used, risks of events are relatively low.

1961 Arterial remodelling in acute coronary syndromes: correlation of intracoronary ultrasound characteristics with temperature of the culprit lesion

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Previous studies have shown positive remodelling of the atherosclerotic plaques in patients (pts) with acute coronary syndromes (ACS). Additionally, involvement of inflammation in the pathogenesis of ACS may lead to heat production. Therefore, we assessed the culprit lesions in pts with effort angina (EA) and ACS by intracoronary ultrasound, and correlated these findings with temperature (T) difference between the atherosclerotic plaque and the healthy vessel wall.
Methods: Twelve coronary lesions of pts with ACS and 13 lesions of pts with stable angina were studied. Lumen and external elastic membrane (EEM) areas were measured at both target lesion and proximal reference sites by intracoronary ultrasound before intervention. The remodelling index was defined as the ratio of the EEM area at the lesion to that at the proximal site. Positive and negative remodelling were defined as indices of >1.05 and <0.95, respectively and plaque area as: EEM area-lumen area at the lesion. Additionally, in all pts T was measured at the culprit lesion and at the normal vessel wall by a thermography catheter that was developed in our institution and the T difference was calculated.
Results: Pts of both groups were similar in age, reference vessel size, and percent diameter stenosis. Positive remodeling was more frequent in pts with ACS (table). In addition there was a good correlation between remodeling index and difference in plaque temperature in pts with ACS ($r=0.68$, $p<0.001$).
Conclusion: The present study showed that the extent of remodeling and the plaque area were greater in culprit lesions in pts with ACS. The association however of remodeling index and plaque area with increased T provides new insights about the involvement of inflammation in the pathogenesis of ACS.

	ACS	EA	P-Value
EEM Proximal Area (mm^2)	14.2±3.6	19.9±9.1	0.07
Plaque Area (mm^2)	12.08±4.1	9.97±3.2	0.05
EEM Stenosis Area (mm^2)	15.5±2.6	19.4±8.7	0.02
Remodeling Index	1.17±0.2	1.01±0.03	0.02
Positive Remodeling	64%	23%	0.001
Negative Remodeling	9%	54%	0.02
T difference	0.22±0.17	0.03±0.03	0.001

1962 Unstable atherosclerotic lesions tend to be disseminated in coronary arteries – Shift from a vulnerable plaque to a vulnerable patient

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Presence of vulnerable atherosclerotic plaque carries adverse prognosis in patients with coronary artery disease (CAD). Since development of unstable lesion depends substantially on systemic factors, it possibly may take place simultaneously in many sites, therefore causing disseminated instability.
Plaque vulnerability has been linked to its positive remodelling (+veR) on intravascular ultrasound (IVUS) and also with complex appearance on angiography.
Therefore we combined IVUS and angiography to assess whether vulnerable plaques are disseminated in coronary arteries.
Methods: Preinterventional IVUS pull back was performed in target lesion of 68 CAD patients (46 males, age 55.6±10,7). Remodeling index (RI) was defined as vessel area at the target lesion site divided by that of average reference segments. The RI>=1.05 was assumed as +veR. Coronary angiograms were analyzed and all plaques >=30% stenosis were classified into complex or smooth groups. Complex plaque was defined if irregularities, ulcerations, total occlusion or thrombus were present and the remaining accounted smooth.
Results: +veR was found in 30 and complex appearance in 15 out of 68 target lesions. Overall angiographically complex plaques were present in 73 out of 163 plaques identified on angiography. Plaques with +veR more often displayed complex angiographic appearance than plaques without +veR (11/30 vs 4/37 respectively; p=0,012) and more often were associated by other complex plaques within the same coronary vasculature (p<0,05, Mann-Whitney test).
Conclusion: Patients with positive remodeling of target lesion display increased number of associated complex plaques in major coronary arteries. This finding suggests that plaque vulnerability, if present tends to be a disseminated phenomenon.

1963 Detection of plaque composition with intracoronary elastography as validated with directional atherectomy

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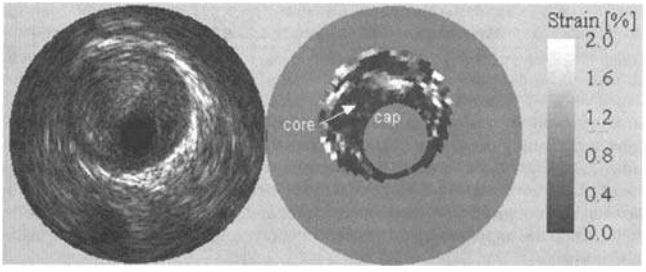
Background: Intravascular Ultrasound (IVUS) Elastography determines the local strain of the vessel wall and plaque. The technique has proven to be able to identify fibrous and fatty plaque components in vitro based on the strain. In this study, intracoronary elastography is evaluated in patients that underwent directional atherectomy.
Methods: Data were acquired in coronary arteries of patients (n=7) referred for PTCA. Cross-sections were investigated with a 20 MHz Visions® catheter (Jomed, Rancho Cordova, CA) to determine the elastograms.
After the elastographic data acquisition, directional atherectomy was performed. A post intervention IVUS was performed to identify the region that was removed. The atherectomy specimens were stained for collagen, fat and macrophages. The plaques were classified as fibrous, fibro-fatty or fatty.
The mean strain of the resected areas was determined and correlated with the plaque type.
Results: The average strain in a fatty plaque (0.34%) was 2 times higher than the strain in fibrous plaques (0.16%). In an artery where a superficial and a deeper cut were performed (see figure), four times lower strain values were found in superficial cap tissue (0.08%) than in core tissue (0.34%). Histology revealed a cap of fibrous material and an atheromatous core containing fat and macrophages.



IVUS echogram and elastogram.

Conclusions: IVUS Elastography results acquired in patients were correlated with histology. Increased strain was observed in plaques containing fat and macrophages. Although exact matching of the atherectomy specimens and the IVUS cross-section remains challenging, this represents the very first attempt to correlate in vivo elastography to histology and these encouraging data warrant further ongoing investigations.

1964 The effect of stenting on the arterial wall temperature. The role of inflammation

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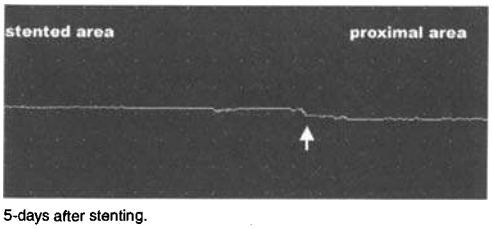
Background: The temperature of the arterial wall has been corelated to its inflammation status. In this study we used thermography to investigate the inflammation status of the arterial wall after stent implantation.
Methods: We catheterized 20 pigs with normal coronary arteries. Arterial wall temperature was studied with the ThermoSense coronary thermography system (Thermocore Medical Systems NV, Belgium) that uses a 4 thermistor-sensor catheter tip. A 60mm long normal segment was selected at the proximal right coronary artery. Temperature was mapped in this segment via a continuous pullback (0,3mm/sec). A 3.0/18mm Freedom stent (Global Therapeutics) was implanted in this area, and temperature was re-scanned. Then, pigs were randomized in two groups: group A to be re-scanned after 5 days and then sacrificed, and group B to be re-scanned after 8 days and then sacrificed. Histology and local macrophage concentration was studied in all cases.
Results: The temperature of the arterial wall before the stent placement was equal to the adjucent areas. Immediately after stent placement, the stented area had slightly lower temperature than the adjucent areas (DT=0,07°C p<0,01). 5 Days after the implantation, the stented area was significantly hotter than the adjucent areas (DT=0,169°C p=0,002); histological examination showed the highest macrophage concentration at the place of the stent. At the ninth day these temperature differences were reduced to non-significant levels (DT=0,002°C p=NS), and macrophage population was significantly lower.
Conclusions: Due to post-stent arterial wall inflammation, stented arterial segments show higher temperature around 5 days after implantation, while after 8 days these findings are back to almost normal levels.



5-days after stenting.

DRUG EFFECTS IN EXPERIMENTAL HEART FAILURE

1966 Molecular and morphological effects of clenbuterol on neonatal rat cardiac myocytes in culture

P.K. Bhavsar[1], L.E. Felkin[1], P.J.R. Barton[1], M.H. Yacoub[2]. [1]*Imperial College, Faculty of Medicine, London, United Kingdom;* [2]*Heart Science Centre, Harefield, United Kingdom*

Background: Optimal recovery from heart failure may require both reverse remodelling and the induction of physiological hypertrophy. We have previously demonstrated that treatment of rats with the beta2-adrenergic agonist clenbuterol results in a 20% increase in LV mass with normal systolic isovolumic parameters and diastolic function. This is accompanied by a 2-fold increase in the expression of atrial natriuretic peptide (ANP) but without changes in gene expression indicative of pathological hypertrophy. For these reasons clenbuterol is regarded as inducing physiological hypertrophy in vivo. However, it remained to be determined whether this is a direct action of clenbuterol on cardiac myocytes. The aim of this study was therefore to determine the molecular and morphological effects of clenbuterol on cardiac myocytes in culture.
Methods: A model system using neonatal rat cardiac myocytes in culture, where the cells are treated with clenbuterol (10μM) or the pathological hypertrophic agonist phenylepherine (PE; 10μM), has been developed. 48 hours after stimulation myocytes were examined under microscope for evidence of morphological change and real-time quantitative PCR (TaqMan) was used to determine expression of genes associated with cardiac hypertrophy. Namely, ANP, brain natriuretic peptide (BNP), alpha and beta myosin heavy chains (MHC), sarcoplasmic reticulum calcium ATPase (SERCA2A) and the glucose transporter GLUT1.
Results: Both clenbuterol and PE induced physical hypertrophy of the cardiac myocytes (1.75 fold increase in surface area as compared to untreated controls, $p<0.05$; N=3) and two fold increase in the expression of both ANP and BNP ($p<0.001$ vs control; N=5). Treatment with PE resulted in a two-fold induction of GLUT1 ($p<0.001$ vs control; N=4) and a three-fold induction of beta MHC ($p<0.001$ vs control; N=5) indicative of a pathological response. In contrast, clenbuterol did not induce any change in expression of alpha or beta MHCs, SERCA2A or GLUT1 (N=4).
Conclusion: We demonstrate that clenbuterol has a direct effect on cardiac myocytes which results in "phyiological" hypertrophic growth. Future studies will investigate the signal transduction pathways invoked during this response.

1967 MCP-1 expression in spontanenous hypertensive rats correlates with blood pressure reduction by angiotensin receptor blockade

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Neurohormonal and cytokine activation occur early in the development of heart failure (HF), yet the potential for these two systems to interact is incompletely defined. Prior studies have shown that in vascular tissues angiotensin II (AII) can upregulate expression of MCP-1, a potent chemoattractant for monocytes, macrophages and lymphocytes. The aim of this study was to establish whether AII antagonism influences MCP-1 expression in myocardium of an animal model of HF (spontaneous hypertensive rats-stroke prone - SHR-SP)

Methods: SHR-SP were randomly assigned to either standard rat chow (SRC), high salt/fat diet (SFD) or SFD with eprosartan (SFD-E), an AII type1 receptor antagonist, via osmotic minipump (25mg/kg/day) for 28 weeks. MCP-1 levels were determined by quantitative TaqMan real-time PCR, ELISA and immunohistochemistry. Macrophage infiltration into myocardium was quantified immunohistochemically as the total area and number (no) of macrophages per eyefield at 100x magnification. Echocardiography was done for cardiac function.

Results: See table.

	SRC	SFD	SFD-E
Mortality at 28 weeks	0%	90%	0%
MCP-1mRNA (copies of mRNA/ng total RNA)	994±140	4169±739*	2696±511#
MCP-1 protein (ng/mg total protein)	76±3	163±33**	71±5
Macrophage area (mm^2/eyefield)	2637±243	5387±700***	1363±331##
Macrophage no	44±4	91±12	23±6
Cardiac output (ml/min)	149±1.2	108.9±9.9**	162.8±5.6

(#p<0.05 vs. SRC), (*p<0.01 vs. SRC), (**p<0.05 vs. SRC and SFD-E), (##p<0.05 compared to SRC and p<0.001 compared to SFD), (***p<0.01 compared to SRC)

Conclusions: MCP-1 was significantly upregulated in this model of HF, and was associated with immune cell infiltration, ventricular dysfunction and disease progression. AII antagonism blunted MCP-1 expression, macrophage infiltration and significantly reduced mortality suggesting a key role for MCP-1 in the mechanism of action of eprosartan. MCP-1 appears to be an important therapeutic target in HF.

1968 Eplerenone, a novel aldosterone receptor antagonist, prevents progressive left ventricular dysfunction and remodelling in dogs with heart failure

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Background: Blockade of aldosterone receptors with spironolactone has been shown to improve survival and reduce morbidity in patients with CHF. In the RALES (Randomized Aldactone Evaluation Study) trial, spironolactone was associated with considerable side effects namely, gynecomastia or breast pain in 10% of patients. Eplerenone (EPL) is a novel aldosterone receptor antagonist that is devoid of these side effects. In this study, we examined the effects of EPL on the progression of LV dysfunction and remodeling in dogs with chronic heart failure (LV ejection fraction 30% to 40%) produced by multiple sequential intracoronary microembolizations.

Methods: Two weeks after the last microembolization, dogs were randomized to 3 months therapy with oral EPL (10 mg/kg twice daily, n=7) or to no therapy at all (Control, n=7). LV ejection fraction (EF), LV end-diastolic volume (EDV), LV end-systolic volume (ESV), LV end-diastolic wall stress (EDWS), and time constant of LV isovolumic relaxation (Tau) were measured before (PRE) and after 3 months of therapy (POST). Treatment effect was based on a comparison of the change in each hemodynamic parameter from PRE to POST between the two groups. Volume fraction of replacement fibrosis (VFRF), volume fraction of interstitial fibrosis (VFIF) and myocyte cross-sectional area (MCSA), an index of myocyte hypertrophy, were measured from LV tissue sections obtained at sacrifice.

Results: Compared to control, EPL prevented the progressive decline in EF (-7±1 vs 0±1, P<0.001) and the progressive increase in EDV (6±1 vs -1±2 ml, P<0.003) and ESV (9±1 vs -1±2 ml, P<0.001). Compared to control, EPL also decreased EDWS (14±5 vs -25±5 g/cm^2, P<0.001) and Tau (6±1 vs. -5±2 msec, P<0.002). Dogs treated with EPL showed a 34% reduction in VFRF, a 37% reduction in VFIF and a 28% reduction of MCSA compared to control (P<0.05).

Conclusion: In dogs with HF, chronic therapy with EPL prevented progressive LV systolic and diastolic dysfunction and attenuated LV remodeling. These findings indicate that EPL may be useful in the long-term treatment of chronic HF.

1969 Long-term heart rate reduction induced by the If current inhibitor ivabradine improves cardiac function and structure in rats with heart failure

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Heart rate reduction (HRR) could be beneficial in congestive heart failure (CHF), since it improves left ventricular (LV) filling and reduces myocardial O2 consumption. However, the effects of selective long-term HRR in CHF are unknown. Thus, we assessed, in a rat model of CHF (coronary ligation), the effects of long-term HRR induced by the selective If current inhibitor ivabradine (10 mg/kg/day as food admix for 3 months starting 7 days after ligation) at the end of the 3 month treatment period and again 3 days after treatment interruption. The table shows heart rate (HR, beats/min), LV systolic pressure (LVSP, mmHg), LV end-diastolic pressure (LVEDP, mmHg), LV dP/dtmax (10^3 mmHg/sec) as well as LV end-diastolic and end-systolic diameters (LVEDD and LVESD, mm), stroke volume (SV, ml/beat) and cardiac output (CO, ml/min) determined in anesthetized rats, using a Millar micro-tip and an echocardiograph (ATL, HDI 5000). After 3 months of treatment, ivabradine decreased LV collagen density (control: 3.4±0.1; ivabradine: 2.9±0.1%; p<0.05) and increased myocardial capillary density (control: 85±6; ivabradine: 103±4 capillaries per field; p<0.05).

Group	HR	LVSP	LVEDP	LVdP/dt	LVEDD	LVESD	SV	CO
1	385±13	133±5	16.8±3.7	7.0±0.5	10.5±0.1	9.4±0.2	0.41±0.03	157±9
2	299±8*	133±7	11.5±4.1	7.6±0.4	10.9±0.2*	8.9±0.3*	0.49±0.03*	162±13
3	388±13†	135±9	20.0±4.1	6.9±0.8	10.7±0.2	8.9±0.2*	0.49±0.02*	177±10*†

Group 1: CHF control; Group 2: CHF + ivabradine; Group 3: CHF after interruption. *: p< 0.05 vs. control; †: p<0.05 vs. ivabradine

In conclusion, in a model of CHF, long-term selective HRR by the If current inhibitor ivabradine improves left ventricular function and increases stroke volume, resulting, despite the HRR, in a preserved cardiac output. This improvement of cardiac function is related to the HRR itself, but also to the modifications of LV structure and/or myocytes properties as a consequence of long-term HRR, since the improvement of cardiac function persists after interruption of the treatment.

1970 Effect of different antiadrenergic interventions on the baroreceptor-heart rate reflex in post-myocardial infarction heart failure rats

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Congestive heart failure (CHF) is characterized by sympathetic overactivity and by an impaired baroreceptor-heart rate reflex (BR-HR). To clarify whether the former alteration plays a causative role on the latter, we examined the effects on the BR-HR of chemical sympathecomy and chronic or acute β-adrenoceptor blockade. CHF developed within 4 weeks of an anterior MI (left anterior descending coronary artery ligation under ether anesthesia in 8 week-old Sprague-Dawley rats, Lig). Lig rats were treated as follows: i) vehicle (Veh-Lig, n=10); ii) chemical sympathectomy by 6-hydroxydopamine, 100 mg kg^{-1} i.p. twice weekly (Sx-Lig, n=11); iii) chronic beta-blockade by oral propranolol, 30 mg kg^{-1} day^{-1} (Pro-ch-Lig, n=6); iiii) acute β-blockade (vehicle alone for 4 weeks and iv Pro, 1 mg kg^{-1}, just before baroreflex testing (Pro-ac-Lig, n=6). Concurrent sham-ligated rats were studied and assigned to vehicle (Veh-Sham, n=10) or 6-hydroxydopamine (Sx-Sham, n=8) treatment. Left ventricular end-diastolic (LVED) dimension was measured by ecocardiography. BR-HR was evaluated by the extent of the bradycardic responses to graded bolus injections phenylephrine in the conscious, chronically instrumented rat. Sympathetic activity was estimated by plasma norepinephrine (NE, by HPLC). LVED dimensions were normal (<7 mm) in all sham-operated rats whereas they were increased (>9.5 mm) in all ligated rats. All groups had similar systemic arterial pressure (systolic range 110-130 mmHg) and heart rate (range 340-380 b min^{-1}) with the exception of the propranolol-treated rats which as expected were moderately bradycardic (305±12 b min^{-1}, pooled Pro-ch and Pro-ac rats, p<0.05 vs all other groups). Plasma NE was similar in all groups (range 150-200 pg ml^{-1}) except in Veh-Lig rats in which it was significantly elevated to 320±35 pg ml^{-1}. Baroreflex-sensitivity (expressed in b min^{-1} $mmHg^{-1}$) was 1.21±0.2 in Veh-Sham rats and was significantly elevated by sympathectomy alone (2.25±0.9 in Sx-Sham rats, p<0.01 vs Veh-Sham); it was drastically reduced by CHF with intact sympathetics (0.38±0.2 in Veh-Lig rats) but was distinctly preserved by CHF plus sympathectomy (1.99±0.9 in Sx-Lig rats). At variance with sympathectomy, chronic β-blockade only partially preserved baroreflex sensitivity (0.81±0.3 b min^{-1} $mmHg^{-1}$ in Pro-ch-Lig rats, p<0.05 vs Veh-Lig) whereas acute β-blockade had no effects (0.40±0.2 b min^{-1} $mmHg^{-1}$ in Pro-ac-Lig rats). Thus sympathetcomy but not β-blockade can virtually entirely prevent the CHF-related impairment of the baroreceptor-heart rate reflex.

1971 Cytosolic Ca^{2+} and force in femoral small resistance arteries from rats with congestive heart failure. Effect of exogenous noradrenaline

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In congestive heart failure (CHF), vasomotor drive to systemic resistance vessels is increased. Postganglionic sympathetic nerves release noradrenaline (NA), which binds to alpha-adrenergic receptors in the cell membrane of vascular smooth muscle cells (VSMC). This initiates a rise in intracellular Ca^{2+} ($[Ca^{2+}]_i$) and VSMC contraction. We evaluated the relationship between $[Ca^{2+}]_i$ and vasoconstriction in six rats with chronic left ventricular myocardial infarction (MI), and six sham operated (SO) rats. Nine weeks post-MI, $[Ca^{2+}]_i$/tension relationships were determined during cumulative administration of NA (10^{-9} - 10^{-4} M) to isolated femoral resistance arteries. We simultaneously recorded isometric tension development and $[Ca^{2+}]_i$, using the FURA-2 method. The CHF rats had infarctions of 48,5 ± 3,5% of the left ventricular internal circumference, measured on cross sections at papillary muscle level. CHF rats showed a 30% increase in ventricular mass (0,29 ± 0,02% of body weight ((BW)) versus 0,23 ± 0,01% in SO rats, $p<0,01$) and a 2,5 times increase in lung weight (0,76 ± 0,06% of BW versus 0,31 ± 0,02% in SO rats, $p<0,001$). No differences were found in baseline $[Ca^{2+}]_i$ between CHF (49 ± 8 nM) and SO rats (48 ±4 nM), nor in the maximum increase in $[Ca^{2+}]_i$ (199 ± 24 nM vs. 167 ± 29 nM in SO rats) or in maximum tension induced by NA (6.01 ± 1.03 N/m vs. 6.27 ± 1.29 N/m in SO rats). See figure. The present data do not support the hypothesis that either baseline $[Ca^{2+}]_i$ or the rise in $[Ca^{2+}]_i$ in response to exogenous NA are altered in resistance arteries of CHF rats compared to those of sham operated rats. These findings suggest that elevation in $[Ca^{2+}]_i$ at a given level of alpha-adrenergic stimulation does not contribute to the increased peripheral resistance in CHF.

NON-LIPID-LOWERING EFFECTS OF STATINS

1972 Statin treatment is associated with reduced heat release from human atherosclerotic plaques in patients with coronary artery disease

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Background: Heat released from atherosclerotic plaques as a result of the local inflammatory process, may be measured in vivo by a thermography catheter. Statins seem to have antinflammatory effect which results in plaque stabilization. The aim of this study was to investigate the effect of statins on plaque temperature.
Methods: The study population included 72 patients (pts): 21 with effort angina (EA), 32 with unstable angina (UA) and 19 with acute myocardial infarction (AMI). Among the study group 37 pts received statins for more than 4 weeks and 35 pts were not receiving statins. We measured temperature difference (TD) between the atherosclerotic plaque and the proximal vessel wall (background temperature) with a thermography catheter, which has been designed and developed in our Institution.
Results: The statistical analysis showed that the mean value of TD was higher in the untreated group compared to the treated, with statin, group (0.56 ± 0.30°C vs. 0.29 ± 0.12°C, $p < 0.01$). Moreover, a progressive increase of TD by type of clinical syndrome was observed in both groups of the study (statin group; EA: 0.24 ± 0.15°C, UA: 0.26 ± 0.26°C, AMI: 0.40 ± 0.28°C, vs untreated group; EA: 0.41 ± 0.26°C, UA: 0.44 ± 0.28°C, AMI: 0.84 ± 0.52°C, $p < 0.05$). Multivariate analysis showed that treatment with statins was an independent factor for temperature variation, after taking into account the effect of clinical syndrome ($p < 0.05$).
Conclusions: Pts under treatment with statins have reduced heat production from the culprit coronary lesion. Thus, statins may have a favorable effect on plaque stabilization. This may be due to an additional anti-inflammatory effect of statins, beyond lipid lowering.

1973 Lovastatin inhibits metalloproteinase secretion by plaque resident cells via a prenylation dependent mechanism-a plaque stabilising effect

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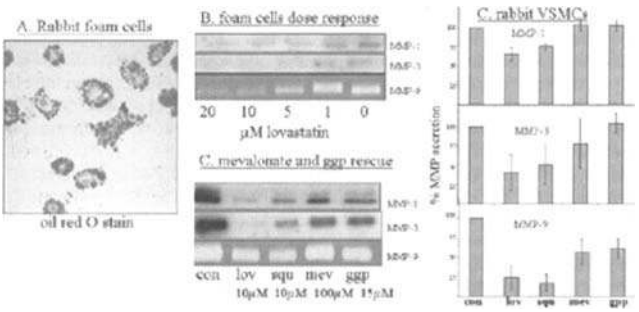
Large clinical trials with HMG-CoA reductase inhibitors (statins) reveal early beneficial effects on cardiac events that are unrelated to angiographically defined regression. This suggests statins may directly affect plaque stability. Recent evidence shows statins reduce production of matrix metalloproteinases (MMPs). Such an effect would tend to preserve plaque collagen content and directly promote plaque stability. We investigated the effect of lovastatin on MMP secretion by vascular smooth muscle cells and foam cells, together the most important source of plaque MMPs.
Methods/Results: Rabbit vascular smooth muscle cells (VSMCs) were generated from aortic medial explants. Rabbit granuloma macrophages were recovered from subcutaneous polyurethane sponges in New Zealand White rabbits fed on a 1% cholesterol diet for 5 weeks. Cultured SMCs and foam cells were treated with different doses of lovastatin and MMP-1 and 3 secretion assessed by western blotting and MMP-9 by gelatin zymography. Lovastatin inhibited secretion of all 3 MMPs in a dose dependent fashion, (Fig.1B). This inhibition was reversed by exogenous mevalonate (meva) and geranylgeranyl-pyrophsphate (ggpp) but not squalene (squ) thus implicating isoprenoid synthesis dependence (Fig.1B,C). Lovastatin did not reduce MMP-1, -3, -9 or Tissue Inhibitor of MMPs (TIMP)-1 and –2 mRNA levels when investigated by RT-PCR.



Conclusion: Lovastatin inhibits metalloproteinase secretion by SMCs and foam cells via a prenylation dependent mechanism implicating the rho GTPases. This lipid-lowering indepent effect of statins may underly their plaque stabilising properties and reduce clinical events.

1974 Atorvastatin decreases Vascular Endothelial Growth Factor (VEGF) – Involvement of inhibited AP-1 and HIF-1 expression

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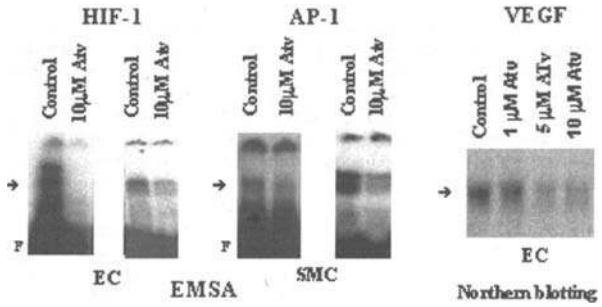
Background: VEGF is suggested to be involved in atherosclerotic plaque growth by inducing neovascularization. HMG-CoA reductase inhibitors (statins) seem to have atheroprotective effects beyond their lipid-lowering properties. The aim of this study was to test the influence of atorvastatin (atv) on VEGF synthesis and transcription factors (AP-1, HIF-1) involved in VEGF gene expression.
Materials and Methods: Human endothelial (EC) and smooth muscle cells (SMC) were treated with different concentrations of atv (1-10μM). VEGF protein and VEGF mRNA (in EC) were assessed by ELISA and Northern Blotting, respectively. AP-1 and HIF-1 DNA binding was determined by EMSA. VEGF plasma levels were measured in 14 patients with coronary artery disease (CAD pts) before and after 2 months of atv therapy (20mg/d).
Results: Atv (1, 3 and 10 μM) treatment resulted in a significant decrease of VEGF release in SMC (59.0±10.4%, 58.4±7.3%, 64.9±5.3% of control cells; $p<0.0005$), which was similarly observed for EC. This reduction of VEGF protein was associated with a significantly attenuated activity of the transcription factors AP-1 and HIF-1 and with a diminished expression of VEGF mRNA (see figure). Furthermore, atv therapy reduced VEGF plasma levels in CAD pts (from 31.1±6.1 to 19.0±3.6 pg/mL; $p<0.05$). Similar results were obtained with simvastatin and lovastatin.



Conclusion: Assuming VEGF to contribute to plaque neovascularization and progression, the observed reduction of VEGF, possibly due to an inhibited AP-1 and HIF-1 expression, may represent a novel beneficial effect of statins.

1975 Atorvastatin decreases platelet superoxide anion production in hypercholesterolemic patients

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Background: Experimental studies have demonstrated that hypercholesterolemia is associated with enhanced cellular production of superoxide anion (O2-). The aim of this study was to assess whether the same phenomenon occurs in humans, too.

Methods: The study was divided in three parts. In the first part of the study we compared 28 patients with polygenic hypercholesterolemia and 25 sex-and-age matched normocholesterolemic subjects. In the second part 21 out of the 28 hypercholesterolemic patients were given atorvastatin 10 mg/day for 8 weeks. Lipid profile and platelet O2- release were measured at baseline and after atorvastatin. In the third part of the study, in order to assess the mechanism by which LDL cholesterol interferes with platelet production of O2-, human platelets were incubated with LDL cholesterol in the presence of either an inhibitor of the phospholipaseA2 enzyme, AACOCF3, or an inhibitor of NADH/NADPH oxidases, DPI.O2- was determined by chemiluminescience using a Bio-Orbit 1251. Platelet aggregation was analized following the Born method.

Results: Platelet formation of O2- was significantly higher in patients(2.11 nmoles/3x108 plts/min) than in controls(1.05 nmoles/3x108 plts/min) ($p< 0.001$) and significantly related to LDL cholesterol ($r=0.88$, $p< 0.001$). In patients with hypercholesterolemia, 8-week administration of atorvastatin 10 mg daily significantly reduced LDL cholesterol (-35%) and platelet production of O2- (-40%). The inhibition of O2- could be explained by atorvastatin cholesterol-lowering effect only to a certain extent, in that it was observed after 3 days of atorvastatin treatment only, and was not parallel to cholesterol reduction. Platelets incubated with LDL cholesterol showed an increased O2- production, which was significantly inhibited by AACOCF3 (-78%) and DPI (-56%).

Conclusions: LDL cholesterol increases platelet O2- production by activating PLA2 and NADH/NADPH enzymes. Inhibition of platelet O2- release by atorvastatin is partially related to cholesterol lowering effect, suggesting that other mechanisms could be responsible for the antioxidant activity of the drug.

1976 HMG-CoA reductase inhibitors promote the translocation of protein kinase Akt to membrane domains in endothelial cells

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Our recent results have shown that the HMG-CoA reductase inhibitors referred to as statins rapidly activate the protein kinase Akt/PKB in endothelial cells (EC) and endothelial precursor cells. This promotes EC survival, nitric oxide production and differentiation in vitro; cellular responses that contribute to new blood vessel growth and stabilization of the vascular network. In vivo, simvastatin was shown to promote collateral and capillary vessel formation in a normocholesterolemic rabbit model of vascular insufficiency. Here, we examine whether statins promote the translocation of Akt to the plasma membrane, an essential feature of Akt activation that is associated with cellular migration. Bovine aortic endothelial cells (BAEC) were transfected with an GFP-Akt (green fluorescent protein) fusion cDNA and then treated with statins under different experimental conditions. Our results show that low doses of simvastatin (0.5μM) rapidly induce the translocation of Akt to discrete sites in endothelial cell plasma membrane. Immunofluorescence microscopy images show that GFP-Akt colocalizes with F-actin-positive, FAK-negative lamellipodia and filopodia, which are essential structures for cellular migration. Translocation was not observed when a point mutation was incorporated in the lipid-binding, pleckstrin homology domain of Akt, demonstrating the specificity of this response. Similar to observations of GFP-Akt localization in transiently-transfected BAEC, endogenous Akt rapidly translocated to discrete sites at membrane ruffles in the simvastatin-treated cells (immunodetection of Akt with anti-Akt1 antibody).

Low doses of pravastatin also induced Akt translocation to membrane ruffles and filopodia. Treatment with L-mevalonate (200 μM) blocked the translocation of Akt by simvastatin. Pretreatment with the phosphoinositide 3-kinase (PI3-kinase) inhibitors LY294002 (7.5 μM) and wortmannin (250 nM) also blocked simvastatin-induced effects on Akt translocation. Finally, our data show that statin-induced translocation of Akt is a specific effect dependent on endothelial cells, because neither simvastatin nor pravastatin had a stimulatory effect on Akt translocation in vascular smooth muscle cells.

The results from this study show that statins induce PI3-kinase-dependent translocation of Akt to membrane structures in migratory cells. These findings, together with the previous results, suggest a new mechanism that can account for the ability of statins to improve endothelial cell function and contribute to new blood vessel growth.

1977 Simvastatin inhibits MMP-9 activity and smooth muscle cell invasion – Prevention of intimal hyperplasia in human saphenous vein

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Basement membrane degradation is a prerequisite for smooth muscle cell (SMC) migration and proliferation in vivo, both of which contribute to the development of intimal hyperplasia (IH) in saphenous vein (SV) bypass grafts. The activity of specific matrix-degrading enzymes produced by the SMC, particularly the gelatinases (MMP-2 and -9), is essential to these processes. HMG-CoA reductase inhibitors (statins) are widely prescribed as cholesterol-lowering drugs but interestingly, also appear to have beneficial effects on vascular SMC function that are independent of their cholesterol-lowering properties.

In organ cultures of the human long SV obtained from patients undergoing coronary artery bypass grafting, neointima formation was accompanied by increased tissue MMP-9 activity, measured by gelatin zymography. Simvastatin (0.5-5 μM), reduced neointimal thickness ($P=0.004$, $n=9$) and concomitant MMP-9 activity ($P=0.03$, $n=6$). Neointima formation in vein grafts requires both SMC proliferation and migration (invasion); we have shown previously that statins inhibit human SV- SMC proliferation. We therefore investigated whether inhibition of MMP-9 activity by simvastatin could reduce SMC migration through a basement membrane barrier (i.e. invasion). Using modified Boyden chambers, we investigated the effects of simvastatin on SMC invasion towards a chemotactic stimulus (10 ng/ml PDGF) over a 24-h period. In this model, SMC gelatinase activity is essential for basement membrane (Matrigel) degradation prior to migration. Simvastatin dose-dependently reduced SMC invasion by 54% (0.5 μM), 69% (1 μM) and 76% (5 μM) of that induced by PDGF alone ($P<0.01$, $n=5$).

Our observations suggest that increased MMP-9 activity contributes to IH in SV grafts. Simvastatin inhibits this response by reducing MMP-9 activity and SMC invasion. Inhibition of HMG-CoA reductase by statins results in reduced intracellular production of mevalonate, not only an essential precursor of cholesterol but also of several isoprenoids that are required for post-translational prenylation of small G-proteins involved in induction of MMP-9 gene transcription. Thus statins may be beneficial in the control of vascular disorders characterised by neointima formation beyond simple reduction of cholesterol.

GENETICS IN ATHEROSCLEROSIS

1978 Identification of a CETP-haplotype associated with low CETP and high HDL-C levels

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Background: The cholesteryl ester transfer protein (CETP) gene is a candidate gene for CAD and several common CETP-polymorphisms have been associated with both CETP and HDL-C levels. To investigate the combined effect of polymorphisms, haplotype effects can be estimated. In the present study, CETP-haplotype effects on CETP and HDL-C levels were estimated using a novel method that also incorporates data of patients with multiple heterozygous genotypes.
Method: Information on four closely-linked CETP-gene polymorphisms (including -629 and TaqIB) and base-line CETP (mean 1.92 ± 0.52 g/l) and HDL-C (mean 0.92 ± 0.22 mmol/l) levels of 884 unrelated male patients with premature CAD of the REGRESS study was used. Based on the individual genotypes per locus (0/0, 0/1 and 1/1), haplotype pairs were assigned to each patient. In case of multiple heterozygous genotypes (49% of the patients), all haplotype pairs compatible with the genotype were determined and posterior probabilities were calculated for each pair using Bayes' theorem and estimated haplotype frequencies. Subsequently, the posterior probabilities were used as weights in a weighted linear regression model.
Results: Base-line CETP and HDL-C levels were not significantly ($P>0.05$) correlated in the REGRESS population. The effects (± SE) of the four most frequent CETP-haplotypes on base-line CETP and HDL-C concentrations are shown in the table. The two most frequent haplotypes (0 0 0 0 and 1 1 1 1) had significant ($P<0.0001$) opposite effects on both base-line CETP and HDL-C concentrations. Furthermore, effects of the least frequent alleles at the different loci appear to be additive. Homozygous carriers of the 1 1 1 1 haplotype are expected to have a 15% lower CETP concentration and a 9% higher HDL-C concentration compared to 0 0 0 0 homozygotes.

Haplotype effects

Haplotype	Frequency	CETP increase (g/l)	(SE)	HDL-C increase (mmol/l)	(SE)
0 0 0 0	53.6%	0.070	(0.015)	-0.020	(0.006)
1 1 1 1	27.3%	-0.080	(0.021)	0.018	(0.008)
0 1 1 1	9.9%	0.000	(0.029)	0.006	(0.010)
0 1 0 0	4.6%	-0.013	(0.032)	0.000	(0.011)

Conclusion: The common 1 1 1 1 haplotype is independently associated with lower CETP and higher HDL-C concentrations in males with premature CAD.

1979 Haplotype analysis of CETP gene polymorphisms in relation with coronary artery disease, HDL-cholesterol and CETP activity in the AtheroGene study

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By catalizing transfer of cholesteryl ester from the core of HDL molecules to apoB containing lipoproteins, in exchange of triglycerides, the cholesteryl ester transfer protein (CETP) plays a key role in the pathogenesis of atherosclerosis. We investigated the relative contribution of CETP gene polymorphisms to the variability of CETP activity and HDL-cholesterol (HDLc) levels as well as their relation to coronary artery disease (CAD). The sample consisted of 1002 patients with documented CAD and 471 controls subjects. Five polymorphisms of the CETP gene were genotyped, one in the promoter region (G-629A), one in intron 1 (TaqIB) and three in the coding sequence (A373P, I405V and R451Q). CETP levels were lower in cases than in controls (38.0 vs 48.8; $p<10^{-4}$) as were HDLc levels (47.6 vs 59.0; $p<10^{-4}$). By univariate analysis, all polymorphisms were associated with CETP activity, explaining from 1.1% to 2.3% of the CETP variability. All polymorphisms were also associated with HDLc levels, explaining from 0.5% to 1% of the HDLc variability. Genotype effects were homogeneous in cases and controls. The -629A allele, which was associated with higher HDLc, tended to be less frequent in cases than in controls (0.44 vs 0.40; p =0.064). Allele frequencies of the other polymorphisms did not significantly differ between the two groups. Since these five polymorphisms were in strong linkage disequilibrium one with each other, an haplotype analysis was performed to better characterize the own contribution of each of them. The haplotype frequency distribution slightly differed between cases and controls (p = 0.044). The haplotype analysis revealed that the -629A and 405V alleles were independently associated with decreased CETP activity. Besides, the A373P polymorphism was shown to interact with the G-629A polymorphism on CETP activity (p = 0.014). The TaqIB and R451Q polymorphisms did not independently influence CETP activity. Jointly, haplotypes combining the G-629A, A373P and I405V polymorphisms explained 6% of the variability of CETP activity. A similar haplotype analysis on HDLc levels revealed that the -629A and 405V alleles were independently associated with increased HDLc levels and jointly explained 2.4% of HDLc variability. None of the other polymorphisms influenced HDL levels. After adjusting for HDLc levels, haplotype frequencies no longer differed between cases and controls (p = 0.13). In conclusion, haplotype analysis showed that several polymorphisms of the CETP gene influenced CETP activity and HDLc levels. The association of polymorphisms with CAD seemed to be mediated by HDLc.

1980 ApoE genotype predicts 90-day and 5-year mortality in male, but not in female, survivors of acute myocardial infarction

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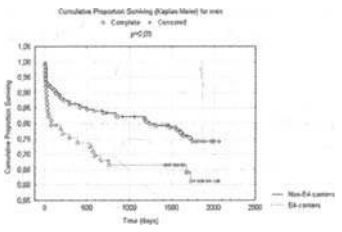
Background: Coronary heart disease (CHD) is caused by a combination of genetic and environmental factors. The ApoE gene polymorphism is known to influence the risk of dying of CHD and appears to play a major role in this interaction. We studied whether ApoE genotype could predict short- and long-term mortality after an acute myocardial infarction (AMI)
Methods: 359 patients (253 men and 106 women) with AMI, consecutively admitted to the coronary care unit, were followed for approximately five years (range 3,8-5,6 years). No exclusion criteria were used. The mean age at the time of inclusion for men was 65,9 years (±12,7 SD, range 34-92) and for women 73,7 (±9,5 SD, range 41-91). ApoE genotype and lipid status were determined and subjects were classified as carriers or non-carriers of the e4 allele.
Results: Apart from lower HDL levels in male e4-carriers, there were no significant serum lipid concentration differencence depending on ApoE genotype. We found a markedly increased mortality in e4-carrying men, with a hazard ratio (HR) of 1,7. The difference was most pronounced during the first 90 days, with a 20,3% mortality among e4-carriers compared to only 8,5% for non e4-carriers (p=0,01). For men in the upper age quartile (>74 years) the deleterious effect of the e4 allele was most obvious, with an adjusted HR of 5,8, for the five year-follow-up. In women apoE genotype had no predictive value on mortality.



Kaplan-Meier graph of survival, men.

Conclusion: The ApoE e4 allele is an important mortality risk factor after AMI in men. The negative impact of the e4 allele seems to be even higher in men over 74 years. The markedly higher risk during the first 90 days may indicate that the ApoE polymorphism affects the stability of the atherosclerotic plaque, making carriers more susceptible to new events.

1981 Polymorphisms of the angiotensin-converting enzyme and interleukin-6 genes interact on long-term prognosis of patients with coronary artery disease

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An I/D polymorphism of the angiotensin-converting enzyme (ACE) gene, which influences plasma and tissue ACE levels, has been reported to be associated with an increased risk of acute coronary syndrome. We investigated the potential association of the ACE I/D polymorphism with long-term prognosis in patients with coronary artery disease (CAD). Since angiotensin II is known to stimulate cellular production of interleukin-6 (IL-6), we also evaluated whether the ACE I/D and the IL6/G-174C polymorphisms might interact to modulate the risk of future cardiac event. The cohort included 1221 patients with proven CAD prospectively followed up during a mean period of 3.4 (maximum 5.2) years. Follow-up information was obtained about death from cardiac causes (n = 83), death from non cardiac causes (n = 33) and non fatal myocardial infarction (n = 51). The ACE/DD genotype (n = 367) was associated with an increased risk of future cardiac event (fatal or non fatal) (HRR, 95% CI = 1.44, 1.02-2.05), but did not influence non-cardiac mortality (HRR = 0.65, 0.28-1.49).
There was an interaction between the ACE I/D and the IL6/G-174C polymorphisms on the risk of future cardiac event. The ACE/DD genotype had no significant effect on risk in subjects with the IL6/GG or GC genotype, whereas in subjects with the IL6/CC genotype, the ACE/DD genotype was associated with a 4-fold increased risk (HRR = 4.26, 1.97-9.23). The interaction was present both in patients with stable angina or acute coronary syndrome at inclusion, and whether or not patients received treatment by beta-blockers or ACE-inhibitors. The ACE I/D polymorphism did not influence serum IL-6 levels, neither directly nor by interacting with the IL-6 polymorphism. This suggests that the interaction between the two polymorphisms might be mediated by a local co-expression of ACE and IL-6 within atherosclerotic plaques. In a sub-sample of 768 patients (63%) in whom ejection fraction (EF) was measured, the two polymorphisms appeared to interact on EF, the ACE/DD genotype having opposite effects on EF according to the IL6 genotype (EF = 61.1% in (GG+GC)/(II+ID), 65% in (GG+GC)/DD, 65.5% in CC/(II+ID) and 58.4% in CC/DD subjects, p = 0.0003 for interaction).
In conclusion, the IL6/G-174C and ACE I/D polymorphisms appear to interact on the long-term prognosis of patients with documented CAD, patients combining the IL6/CC and ACE/DD genotypes having the worst prognosis. This interaction is consistent with the notion that angiotensin II may contribute to the development of acute coronary syndromes through an inflammation-mediated process.

1982 The RANTES chemokine-403A polymorphism is associated with an increased risk of coronary artery disease and venous thrombo-embolism

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Circulating platelets and chemoattractant cytokines (= chemokines) such as RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted) play a major role in the activation of monocytes and endothelium, as well as in the recruitment of leukocytes into atherosclerotic plaques. RANTES deposition by platelets trigger monocyte arrest on inflamed and atherosclerotic endothelium. Therefore, RANTES may play an important role in the pathogenesis both of atherosclerosis and thrombosis. The -403A polymorphism in the RANTES promoter results in a new consensus binding site for GATA transcription factors and a ~8-fold increase in transcriptional activity. In the present study, we have tested the hypothesis that this polymorphism is associated with an increased risk both of coronary artery disease (CAD) and of venous thrombo-embolism (VTE). Because smoking alters platelet function, analysis was carried out in smokers and non-smokers.
Methods: Patients (pts.; n = 3,194) underwent coronary angiography because of stable angina or atypical chest pain. Genotyping was done by RFLP-PCR. Statistical analysis was done by the Fisher-exact test; odds ratios (95% CI) are given.
Results: Based on coronary angiography, pts. were subdivided into a CAD group (n = 2,689; age: 63.8 ± 10; smokers: n = 1,823) and a control group (C) with normal coronary arteries (n = 505; age: 56.7 ± 11.9; smokers: n = 237). The RANTES -403A allelic frequency was as follows: CAD = 0.200 vs. C = 0.172; p = 0.047; OR 1.20 (1.006-1.342). In smokers, the -403A allelic frequency was as follows: CAD = 0.194 vs. C = 0.152; p = 0.031; OR = 1.35 (1.035-1.755). In the CAD group, a history of VTE was found in 169 pts., but not in 2,520 pts. (= no-VTE). The -403A allelic frequency was as follows: VTE = 0.248 vs. no-VTE = 0.196; p = 0.025; OR = 1.35 (1.042-1.535); VTE vs. C: p = 0.003; OR 1.59 (1.182-2.136). In non-smokers, the -403A allelic frequency was as follows: VTE = 0.295 vs. no-VTE = 0.205; p = 0.019; OR = 1.63 (1.098-2.412).
Conclusions: The RANTES -403A polymorphism is associated with an increased risk of coronary artery disease, particularly in smokers. In CAD patients, this polymorphism is also associated with an increased risk of venous thrombo-embolism, which is more evident in non-smokers. These results suggest a significant role of RANTES in the pathophysiology both of coronary arteriosclerosis and venous thrombo-embolism, which may be due to enhanced RANTES expression in atherosclerotic lesions and increased RANTES deposition by activated platelets.

1983 A PPARα gene polymorphism is associated with myocardial infarction in individuals with positive family history

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Peroxisome proliferator-activated receptor a (PPARa) is a transcription factor involved in lipid metabolism, hemostasis, and inflammation. With respect to atherosclerosis, PPARa has been involved in expression of VCAM-1, tissue factor, and IL-6 levels; its role in the pathogenesis of myocardial infarction (MI), however, is unclear. We therefore investigated the association of a newly identified polymorphism in intron 7 (C2528G) with MI. To enhance the genetic component, we focussed the study on subjects with a positive family history.
Methods: We examined 6380 individuals by complete pheno- and genotyping. 1) MI families with at least two affected individuals (index patients suffering from MI <60 years)[n=968], 2) affected siblings [n=962], 3) non-affected siblings [n=888], 4) married-in spouses from MI families [controls; n=1114]. The findings in MI families were contrasted to 5) sporadic MI patients [n=582] and 6) participants of a population-based survey [n=1866].
Results: The overall allele frequency was in Hardy-Weinberg equilibrium but differed markedly between MI family members and married-in spouses (p<0.0001), but not between sporadic MI cases and survey controls. Between PPARa genotypes, there was no relevant difference in risk factors, such as systolic, diastolic blood pressure, cholesterol and its subfractions, in anthropometric or in history data (age at MI, age at inclusion, time between MI and examination).

Frequency of PPAR genotypes

Population	Total n=	CC, %	CG, %	GG, %	P vs. controls
MI index patients	968	80,0	17,6	2,5	< 0,0001
affected siblings	962	84,3	13,4	1,1	< 0,0001
non-affected siblings	888	84,7	13,6	1,7	< 0,0001
Controls	1114	67,1	29,9	3,1	
Sporadic MI patients	582	69,9	26,3	3,8	n.s.
Survey	1866	68,2	28,5	3,3	n.s.

Conclusion: The PPARa polymorphism is highly significantly associated with MI in individuals with a strong familial component as compared to both, sporadic MI cases, married-in spouses and population-based controls. The high condensation of potentially pathogenic alleles in individuals with a positive family history allows to detect disease-related genetic variants that may escape detection in an unselected sample.

STUNNING, HIBERNATION, PRECONDITIONING

1984 Activation of ATP-dependent potassium channels is trigger but not mediator of ischaemic preconditioning in pigs

P. Gres, R. Schulz, A. Skyschally, G. Heusch. *University of Essen, Pathophysiology, Essen, Germany*

Blockade of ATP-dependent potassium channels (KATP) with glibenclamide starting before the preconditioning ischemia and continued until the end of the index ischemia inhibits the reduction of infarct size by ischemic preconditioning (IP) in pigs (Am J Physiol 267: H1341-H1352, 1994). Studies in isolated buffer-perfused rabbit hearts suggested that activation of mitochondrial KATP may act as trigger rather than mediator of IP (Circ Res 87: 460-466, 2000). However, pigs are much closer to humans with respect to coronary blood flow and infarct development. Whether activation of KATP acts as trigger or mediator of IP in pigs in situ, is not yet known.

In 35 enflurane-anesthetized pigs the LAD coronary artery was perfused from an extracorporal circuit. Subendocardial blood flow (ENDO, ml/min/g, microspheres) and infarct size (IS, %, TTC) were measured. After 90 min of severe ischemia and 120 min reperfusion IS was 24.2±3.4 [SEM] (n=7 ENDO:0.045±0.009). IS was reduced to 6.5±5.6 ($p<0.05$, n=7, ENDO:0.048±0.026) by IP with one cycle of 10 min ischemia and 15 min of reperfusion. Glibenclamide given intravenously (0.5 mg/kg as a bolus followed by 50μg/min continuous infusion until the end of the index ischemia) did not change IS per se (20.0±2.3, n=7, ENDO:0.040±0.006). Whereas glibenclamide starting before the preconditioning ischema inhibited the infarct size reduction of IP (see above), its application starting just prior to the index ischemia did not affect infarct size reduction by IP (9.2±5.5, n=7, ENDO:0.045±0.010). Heart rate, left ventricular pressure and area at risk were comparable among the groups.

Conclusion: Activation of KATP acts as trigger and not mediator of infarct size reduction by ischemic preconditioning also in pigs in situ.

1985 Scavenging of free oxyradicals by ascorbic acid attenuates ischaemic preconditioning in pigs

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The involvement of free oxyradicals in the signal transduction of ischemic preconditioning has been established in rats and rabbits. Data from larger mammals such as pigs in which the coronary circulation and infarct development are closer to that in man are lacking. We have therefore investigated the impact of the natural radical scavenger ascorbic acid on ischemic preconditioning in pigs.

In 32 anesthetized pigs the LAD coronary artery was perfused from an extracorporal circuit. Subendocardial blood flow (BF; ml/min/g; radioactive microspheres) and myocardial infarct size (% area at risk; TTC-staining) were determined.

In animals undergoing 90 min severe ischemia and 120 min reperfusion the infarct size averaged 26.9±3.9% (Mean±SEM; n=9; BF:0.048±0.070). Ischemic preconditioning by 10 min ischemia followed by 15 min reperfusion reduced infarct size to 6.4±2.4% (n=9; BF: 0.054±0.011; $p<0.05$).

The infusion of ascorbic acid (i.v.; 2g bolus/maintenance dose 25mg/min until the end of ischemia) starting 30 min before ischemia had no effect on infarct size per se (n=5; 24.0±7.7%; BF: 0.053±0.014). The same dosage of ascorbic acid given 30 min before the preconditioning ischemia largely abolished the infarct size reduction by ischemic preconditioning (n=9; 19.1±5.4%; BF: 0.046±0.010).

Group	Infarct size % Area at risk	Subendocardial blood flow ml/min/g
I/R (n=9)	25.5 ± 3.8	0.048 ± 0.01
IP+I/R (n=9)	5.2 ± 1.7 *	0.057 ± 0.01
A+I/R (n=3)	29.0 ± 4.7	0.044 ± 0.03
A+IP+I/R (n=9)	19.1 ± 4.0	0.045 ± 0.03

We conclude that scavenging of free oxyradicals with ascorbic acid attenuates the beneficial effect of ischemic preconditioning on infarct size in pigs. Therefore, free oxyradicals are also involved in the signal transduction cascade of ischemic preconditioning in pigs. Whether they act as triggers or mediators of ischemic preconditioning remains to be elucidated.

1986 Not only PKC activation after PC but also duration of ischaemia that induces myocardial stunning determine the anti-stunning effects of late PC

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In contrast to the effect of ischemic preconditioning (PC) on infarction, the phenomenological features of the late PC effect on myocardial stunning have not been well characterized. In this study, we assessed the roles of PKC-epsilon (a key kinase of PC) and the difference in anti-stunning effects of late PC depending on how myocardial stunning is induced. Methods: Rabbits were chronically instrumented with a balloon occluder around a circumflex artery and with a Doppler sensor in the circumflex region to monitor the thickening fraction (TF). Since post-infarct ventricular remodeling prevents PC from activating PKC-epsilon (Miki et al. Circulation 2001;104:II-209), we induced ventricular remodeling by ligating the left anterior descending artery in some rabbits to use them as a model of PKC dysfunction. Two weeks after surgery, conscious rabbits underwent either of two ischemia (I)/reperfusion (R) protocols (I/R-1 and I/R-2) on day 1 and day 2. I/R-1 and I/R-2 consisted of 5 cycles of 5-min I/5-min R and 3 cycles of 8-min I/5-min R, respectively. In pilot experiments, we confirmed that I/R-1 and I/R-2 induced the same degrees of severity of stunning despite the difference in the durations of ischemic episodes. Using separate rabbits, myocardial tissues were sampled for Western blotting of PKC. Results: Both I/R-1 and I/R-2 similarly increased the membrane fraction of PKC-epsilon from 52±3% in a non-ischemic condition to 61±3% and 74±3% of the total, respectively (both $p<0.05$). I/R-1 on day 1 significantly improved recovery from I/R-1 on day 2 (Total deficit of TF during 2-hr reperfusion [defTF] was 45% on day 1 vs. 37% on day 2, $p<0.05$.), but I/R-2 on day 1 failed to attenuate the stunning by I/R-2 on day 2 (defTF: 46% on day 1 vs. 44% on day 2, p = ns). I/R-1 on day 1 also failed to attenuate the myocardial stunning induced by I/R-2 on day 2 (defTF: 46% vs. 46%, p = ns). In the rabbits with post-infarct ventricular remodeling, PC induced neither PKC-epsilon translocation nor late PC effects (defTF after I/R-1: 41% on day 1 vs. 39% on day 2). Conclusions: The results support the notion that PKC-epsilon is necessary for the anti-stunning effect of late PC. The finding that a modest prolongation of each ischemic episode (i.e., from 5 to 8 min) did not change the severity of myocardial stunning but made the stunning refractory to late PC suggests that late PC primarily enhances tolerance against ischemic injury rather than reperfusion injury per se.

1987 Additional low dose dobutamine stress imaging is superior to magnetic resonance scar imaging (late enhancement) alone for the prediction of functional recovery

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Background: Recently, new MR techniques (late enhancement) have been shown to yield a high value for the prediction of functional recovery of hibernating myocardium (HM). Other methods (echocardiography [Echo] or magnetic resonance [MR]) using low dose dobutamine (5-10μg/kg/min) have been successfully used in clinical routine for years. The scope of this study was to determine the additional value of dobutamine stress Echo and MR in relation to late enhancement for the detection of HM.

Methods: In 26 consecutive patients with coronary artery disease (67±8 yrs, 3 female, EF 35±7%, wall motion score index 2.1±0.4), scheduled for revascularisation (PTCA 23, CABG 2) wall motion was evaluated semi-quantitatively (16-segments) by Echo and MR (Philips ACS, NT, 1.5 Tesla) before and 3 months after intervention. MR scar imaging (late enhancement; Gd-DTPA) was performed before revascularization and the transmural extent of scar was assessed. The analysis was based on 171 segments with wall motion abnormalities at rest.

Results: The majority 89% of the 72 segments with improved wall motion after revascularization was found in segments with <50% transmural extent of scar. Subgroup analysis with respect to the transmural extension of scar was performed. The results concerning the additional value of stress imaging by MR or echo for the diagnosis of HM in these subgroups are summarized in the table.

	M_PV+	M_PV-	M_LHR	M_P	E_PV+	E_PV-	E_LHR	E_P	N	PreV
no scar	0.74	0.67	10.1	0.001	0.71	0.54	3.7	0.05	61	0.56
scar<50%	0.77	0.81	26.9	<0.001	0.53	0.62	1.1	n.s.	74	0.43
scar>50%	-*	0.86	3.7	n.s.	-*	0.82	3.2	n.s.	36	0.17

M_ MR, E_ echo, PV+ positive predictive value, PV- negative predictive value, LHR likelihood ratio, P p-values, N number of segments of subgroup, PreV prevalence of HM in subgroups, -* positive predictive values are not valid as a result of the low prevalence of HM in this subgroup.

Conclusions: Especially in the subgroup of patients with scar < 50% additional dobutamine stress testing improves predictive value for hibernating myocardium. In this group, stress MR is superior to stress echo. In the subgroup of patients with scar > 50% of the wall thickness dobutamine stress testing does not improve diagnosis.

1988 Assessment of myocardial hibernation in patients with left ventricular dysfunction, coronary disease and type II diabetes

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A number of techniques delineate hibernating myocardium (HM) including dobutamine echocardiography (DE) that identifies contractile reserve and positron emission tomography (PET) that measures myocardial glucose uptake (MGU) using 18F-fluorodeoxyglucose (FDG). Myocardial insulin resistance is present in patients with coronary artery disease (CAD) and may be amplified in those with type II diabetes (DM). The relationship between MGU and inotropic response to dobutamine in dysfunctional but viable myocardium is unknown in type II diabetes. We therefore measured MGU and performed DE to assess myocardial viability in patients with impaired LV function and CAD referred for bypass surgery (CABG). PET and DE were analysed using a comparable 16 segment LV model. The definitions of viability were MGU >0.25μmol/min/g and improvement in wall motion of >1 grade at DE. HM was defined by functional improvement at echocardiography 6 months after CABG.

Patients and Methods: 55 patients (aged 62.0±9.0 yrs, 19 type II DM) with significant LV dysfunction and multivessel CAD were studied. Baseline LV ejection fraction (LVEF), resting wall motion score index (WMSI) and WMSI with dobutamine were similar in non-DM and DM patients (26.7±11.0% vs. 28.2±11.2%, 2.37±0.72 vs.2.24±0.67 and 1.59±0.52 vs.1.51±0.4 respectively, all p=ns).

Results: At DE, the number of dysfunctional viable segments per patient was similar irrespective of DM. However, a MGU of 0.25 μmol/min/g identified fewer segments as viable although patients with type II DM subsequently displayed a similar improvement in LV function following CABG (table).

	No diabetes	Type II diabetes	P
DvS PET	10.8 ± 4.0	7.8 ± 4.7	<0.01
DvS DE	10.7 ± 3.6	10.2 ± 4.2*	ns
LVEF 6months post CABG	37.2 ± 15.6	35.0 ± 11.5	ns
WMSI 6 months post CABG	1.72 ± 0.7	1.83 ± 0.62	ns

DVS: dysfunctional viable segments*: P<0.01 vs DVS PET in type II diabetics

Conclusions: PET may underestimate the extent of hibernating myocardium in type II DM. Clarification of the threshold value defining viability is required in order to optimise the identification of such patients who may benefit from revascularisation.

MONITORING ATRIAL SEPTAL DEFECT CLOSURE BY ECHOCARDIOGRAPHY

1989 TEE guidance of transcatheter ASD/PFO closure

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Transcatheter occlusion of PFO/ASD has become a popular, safe and effective alternative for surgery. The cornerstone of this therapeutic procedure is TEE guidance.

Objectives: The role of TEE and its efficacy were prospectively assessed in a series of 104 consecutive patients who were considered for transcatheter occlusion of interatrial shunts.

Patients & Methods: 44 patients (20F, 24M), mean age 50.5 (25-77)yrs, were referred due to a cryptogenic TIA/CVA. All PFO's were successfully occluded on first attempt (100%) with 10 CardioSeal/StarFlex, 1 Cardia and 33 Amplatzer devices.

60 patients (39F, 21M), mean age 25 (3.9-70)yrs, were referred due to an ASD diagnosed by TTE. 8 were found by TEE to have an unsuitable anatomy for device occlusion: 6 - huge (>36mm) defects, 1 - sinus venosus defect, 1 - severe mitral valve disease. The remaining 52 patients underwent successful occlusions with 7 CardioSeal/ StarFlex and 45 Amplatzer devices.

A single case of pericardial effusion has occurred during the early learning curve. There were no other immediate or late complications, median follow-up 15 (2-32) months.

Overall procedure time = 34 (17-65)min, fluoroscopy = 7 (2-11)min.

TEE imaging: HP-2500/4550, pediatric biplane transducer.

Results: 1. TEE has effectively guided all steps of the procedures.

2. TEE has accurately measured the exact size of all defects:

Mean TEE diameter = Fluro (!)

PFO nonstretched diameter = 5.16(3-9)mm, stretched = 11.6(8-15)mm,

ASD nonstetched = 12.1(8.8-25)mm, stretched = 19.8 (15-35)mm;

3. TEE has identified in detail the characteristic anatomy of each individual defect. Multiple defects were noted in 8 patients, all sucessfully treated with a single device.

4. TEE has enabled validation of optimal proper device placement.

5. Trivial color flow leaks were often detected by TEE at the end of the procedure (mostly through the occluding device and less often through its rims), yet no residual shunt was detected 1 week later.

6. TEE has identified in real-time the accumulation of pericardial fluid and enabled early dainage.

Conclusions: 1. TEE guidance is providing all the essential data for optimal device selection and performance of transcatheter PFO/ASD closure with minimal or no fluoroscopy.

2. Usage of a small pediatric TEE transducer is advantageous in adult patients undergoing this procedure and is not associated with decreased resolution.

3. Transcatheter PFO/ASD occlusion is a team-work effort requiring full and close cooperation between the echocardiographist and the interventionalist.

1990 The role of transoesophageal echocardiography to choose Amplatzer occluder device size in adult patients with secundum atrial septal defect

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Transcatheter closure of secundum atrial septal defect (ASD) with Amplatzer septal occluder (ASO) device is a safe and effective alternative to surgical closure in the adult population. Trans-esophageal echocardiography (TEE) provides important information in the selection of patients eligible for ASD closure device. However, ASO size is selected using stretched defect diameter or intracardiac echocardiography. The aim of this study is to investigate whether TEE enables precise determination of ASO device size.

Methods and Results: Between May 1999 and September 2001, 36 adult patients (21 female, mean age of 44.6+15.1 years) with ASD were evaluated by multiplane-TEE for percutaneous closure with ASO-device. Anatomical ASD diameter (edge-to-edge ASD borders), atrial septum length and ASD rims were measured by TEE. Moreover, rim thickness of 2.5 mm around the defect was selected as reference and a new diameter (procedural ADS diameter) was measured using the new borders. Stretched diameter was calculated.

The mean anatomical ASD diameter was 14.4+7.2mm (range 4 to 23 mm). The mean procedural ASD diameter measured 19.3 +8.3 mm (range 7 to 33 mm) and stretched defect diameter measured 19.5+8.4 mm (range 8 to 34 mm). ASO-device size was 19.8+ 8.2 mm (range 8 to 34 mm). The anatomical ASD diameter underestimated the ASO-device size by 5.4 mm ($p < 0.001$). Whereas, a good linear correlation between procedural ASD diameter ($r= 0.99$) and between stretched defect diameter and ASO size ($r= 1$) was assessed. Atrial septum length was 53.1+6.5 mm and the difference between atrial septum length and ASO-device diameter was 33.3 mm. ASO-device was implanted successfully in 94.4% (34/36) of patients. In 2 (5.6%) cases ASO closure failed because the defect was too large. In none patient obstruction of anatomical structures (Vena Cava, atrio-ventricular valves and venous sinus) was shown by TEE.

Conclusions: 1. Procedural ASD diameter measured by TEE enables precise determination of ASO device size and can be used instead of stretched defect diameter with reduction of time and cost of procedure 2. Adequate atrial septum lenght has to be present to avoid structural obstruction.

1991 Comparison of 2D and 3D transoesophageal echocardiography with the stretching balloon maneuver for atrial septal defect measurement

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Transcathether device closure has become a successful alternative to surgical repair of atrial septal defect (ASD). Information obtained by two-dimensional transesophageal echocardiography (2DTEE) play an important role in patient selection and ASD closure monitoring. However, 2DTEE often underestimates stretching balloon (SB) diameter, and the choice of device size is therefore based on invasive measurement. Three-dimensional TEE (3DTEE) measurements of ASD demonstrated to closely correlate to SB diameter. However, some ASD may be underestimated even with this new technique.

Aims: to compare side-by-side 3DTEE and BS measurements of ASD and to elucidate the anatomical characteristics of the atria and atrial septum that may lead to ultrasound vs. invasive underestimation.

Methods: forty ASD pts undergoing transcatheter closure with the Amplatzer device were enrolled in the study. 2DTEE monitoring, 3DTEE reconstruction and stretching balloon (SB) evaluation of the defect were performed in each patient. 3DTEE maximal diameter (3DD) and SB diameter (SBD) were compared. Left atrium area (transthoracic echocardiography), atrial septal thickness, systo-diastolic motility of fossa ovale tissue (2DTEE), septal defect maximal and minimal rim length and percent change of systo-diastolic defect area (3DTEE) were also measured.

Results: SBD (20.8±7 mm) and 3DD (19.6±6 mm) correlated significantly ($r=0.83$, E.S.=0.7 $p<0.001$). The systematic error (bias) between 3DTEE and SB values was 1.18 ± 4 mm (underestimation). Pts were divided in Group 1 (n=28) in which SBD - 3DD difference was lower than 1SD (4 mm), and Group 2 (n=12) in which SBD - 3DD was > 4 mm. No difference was found in echocardiographic data between the two groups, with the exception of atrial septal motility that was significantly higher in Group 2 (8.3±2.3 vs. 4.2±1.7 mm, $p<0.01$). All Group 1 pts had atrial septal motility < 6 mm, while 80% of Group 2 pts showed atrial septal mobility > 6 mm.

Conclusions: atrial septal motility and elasticity can affect echocardiographic accuracy in ASD size evaluation. Underestimation of echocardiographic vs. SB ASD sizing is likely due to increased balloon stretching of the fossa ovale tissue in pts with these anatomical features.

1992 Improved quantification of atrial septal defect size using transthoracic three-dimensional echocardiography before Amplatzer closure

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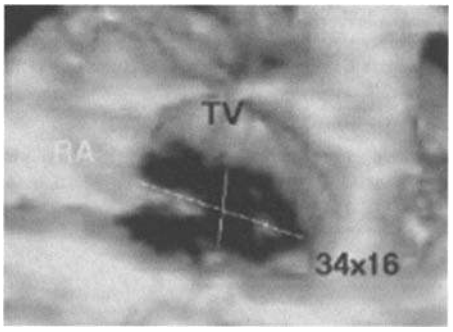
The aim of the study was to compare the usefulness of transthoracic three-dimensional echocardiography (3D) with transesophageal 2-dimensional echo (TEE) for the estimation of secundum atrial septal defect (ASD) dimensions, before interventional closure of defect with Amplatzer device.

Method: 16 children and young adults (3-20 years, 11±6) were studied prior to Amplatzer device implantation using 3D and TEE. 3D was performed using rotational acquisition at 3degree intervals from transthoracic windows (TomTec Echoscan 3.0). Long and short diameter of defect predicted mean diameter and area were by TEE and 3D. Results of measurements were compared to stretched balloon diameter and final Amplatzer waist diameter. All patients underwent successful implantation procedure without residual leaks after 6 months.

Results: Quality of 3D was good in 11 pts and satisfactory in 7. Mean stretched/Amplatzer diameter was 20±5/22±5mm and stretched/Amplatzer waist area 3.2±1.8/3.9±2.0 cm^2. Maximal diameters were severely underestimated by TEE and not by 3D: 14±4 vs 23±5 mm ($p<0.001$), with calculated areas of 1.2±0.6 vs 2.9±1.5cm^2 resp. ($p<0.001$). The results of 3D had good correlation and close agreement in Bland-Altman analysis to stretch diameter (r=0,87) with small underestimation of true size of implanted device by 3mm. TEE results underestimated defect size markedly (r=0,59, underestimation >6mm).



Conclusions: Transthoracic 3D is a feasible technique in young patients, and, as opposed to TEE, allows accurate transthoracic measurements of ASD diameter and reliable prediction of necessary Amplatzer size in young patients. 2-dimensional measurements suffer from significant underestimation of defect dimensions.

1993 Intracardiac echocardiography in the diagnosis and treatment of atrial septal defect and patent foramen ovale

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Purpose: Traditional implantation method of Amplatzer devices for closure of interatrial communications uses balloon sizing (SBS) and transesophageal echocardiography (TEE). We propose a new method using intracardiac echocardiography (ICE) alone for the selection of the prosthesis and the monitoring of the procedure.

Materials and methods: Eighty consecutive patients (mean age 46.4±16.1 years) underwent transcatheter closure of atrial septal defect (ASD, 45 patients) or patent foramen ovale (PFO, 35 patients) using the Amplatzer devices. ICE was used for confirming the diagnosis, excluding the presence of associated anomalies, device size selection and monitoring of the procedure. ICE examination was standardized, defining 5 views (4 transverse and one longitudinal). Devices were selected aiming at full fossa ovalis coverage. Patients underwent transthoracic echocardiography (TTE) prior to discharge and at 3 months and TEE at 1 year.

Results: Transcatheter occlusion was successful in all patients and no periprocedural complications. In patients treated for ASD, mean defect diameter on ICE was 28.4±6.5 mm and mean device size was 28.8±5.6 mm. Complete occlusion was seen in 98,2%, 99,2% and 100% at predischarge TTE, 3 months-TTE and 1 year TEE respectively. Complete occlusion was seen in 100% of patients with PFO on predischarge TTE. In 48.5% associated septal aneurysm was seen. ICE also proved to be adequate in the evaluation of associated anomalies and in the monitoring of the deployment of the devices using the longitudinal 4 chamber view. In no cases were devices oversized, undersized or misaligned to the septum.

Conclusions: ICE-guided device selection and deployment aiming at full fossa ovalis coverage is safe and feasible. It increases patient comfort and acceptance of the procedure and can provide an effective alternative to TEE and stretched SBS.

1994 Right heart reverse remodelling after transcatheter closure of atrial septal defect

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Atrial septal defect (ASD) is one of the most common congenital cardiac abnormalities. The pathophysiologic consequences of ASD result from left-to-right shunting with an increase in pulmonary blood flow and right heart volume overload. ASD closure corrects these hemodynamic abnormalities. The following study was conducted to analyze changes of right heart geometry following transcatheter ASD closure.

Twenty-seven patients (11 men, 16 women) underwent transcatheter closure of a secundum-type ASD with the Amplatzer septal occluder (median size 24 mm) at the age of 43 ± 15 years. All patients had a pulmonary-to-systemic flow ratio by oximetry (Fick method) of at least 1.5:1 and 22 of 27 patients had ASD-related symptoms. Color Doppler transesophageal echocardiography demonstrated complete occlusion without residual shunt in 26 patients and a small residual left-to-right shunt in one patient at 6 months. All patients underwent a complete transthoracic echocardiographic study before and 6 months after ASD closure. Measurements were performed in the apical four-chamber view. Right atrial area at end-systole (planimetry) decreased from 21.1 ± 5.5 cm^2 to 17.3 ± 4.4 cm^2 ($P<0.0001$). Right atrial volume (area-length-method) changed from 64 ± 24 ml to 47 ± 20 ml ($P<0.001$). Right ventricular end-diastolic diameter (inflow tract) decreased from 3.8 ± 0.4 cm to 3.3 ± 0.3 cm ($P<0.0001$). Right ventricular end-diastolic volume (RVV) was approximated by calculating the total volume of both ventricles and then subtracting the combined volume of the left ventricular cavity and interventricular septum. RVV decreased from 201 ± 51 ml to 149 ± 37 ml ($P<0.0001$). Right ventricular (RV) fractional area change as a measure of RV function did not change significantly (29.9 ± 6.0% to 32.2 ± 5.2%, P=NS).

Transcatheter closure of ASD corrects the hemodynamic abnormalities and causes regression of right heart volume overload at 6 months. This process may be related to the symptomatic improvement following ASD closure.

INFLAMMATION, CYTOKINE AND HEART FAILURE

1995 In vivo inhibition of tumor necrosis factor-alpha alleviates oxidative stress and reduces myocyte apoptosis in experimental heart failure

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The pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) is known to induce oxidative stress and trigger apoptosis in vitro. Robust expression of TNF-alpha, increased oxidative stress and apoptosis have been observed in the failing heart. Accordingly, the current study tested the hypothesis that TNF-alpha induced oxidative stress and apoptosis in vivo and therefore contributed to progressive LV dysfunction in heart failure (HF).
Dogs were randomly assigned to: 1) no pacing (controls, n=10), 2) chronic RV pacing for 4 weeks to severe HF (HF, n=10), and 3) pacing with concomitant treatment with etanercept, a chimeric TNF-alpha soluble receptor, 0.5 mg/kg twice weekly SC (HF-etanercept, n=10). Oxidative stress was assessed by LV tissue total aldehyde level measured using gas chromatography/mass spectroscopy and apoptosis was quantified using photometric enzyme immunoassay for cytoplasmic histone-associated DNA fragments (cell death ELISA). LV ejection fraction (LVEF) was assessed by echocardiography.
LV tissue total aldehyde level and absorbance for DNA fragments increased markedly in HF, signifying the presence of severe oxidative stress and increased apoptosis. This was accompanied by a significant reduction in LVEF, reflective of severe LV dysfunction. Treatment with etanercept normalized LV aldehyde levels, reduced absorbance for DNA fragments in the myocardium, and partially restored LVEF.

Effects of etanercept

	Control	HF	HF-etanercept
LVEF (%)	53 (2)	19 (3)*	26 (2)**
Aldehydes (pmol/100 mg)	7048 (448)	11760 (1410)*	6991 (516)**
Cell death ELISA (units)	0.62 (0.08)	1.26 (0.15)*	0.79 (0.10)**

Data, means (SE); * $p<0.05$ vs controls, ** $p<0.05$ vs HF

Our data demonstrate an important role of TNF-alpha in canine pacing-induced CHF. Specifically, increased TNF-alpha contributes to LV dysfunction, which is mediated in part by a local increase in oxidative stress and apoptosis in the failing heart.

1996 Decreased levels of the anti-inflammatory cytokine interleukin-10 in patients with chronic heart failure

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Background: Inflammation plays a significant contributory role in the pathogenesis of chronic heart failure (CHF). Previous data showed enhanced plasma levels of proinflammatory cytokines (i.e. TNF-alpha, IL-6) as well as persistent immune activation in patients with CHF. However, little is known about the regulation of antiinflammatory cytokines such as interleukin (IL)-10. IL-10, which is expressed in human atherosclerotic plaques, has potent deactivating properties in macrophages and T cells and thus acts as a down-regulator of cell-mediated immune responses. The aim of the present study was to assess whether serum concentrations of IL-10 significantly differed between patients with CHF and healthy control subjects.
Methods and Results: 33 patients with chronic heart failure (67.7 ± 11.2 years, mean ejection fraction 20.9+7.0%, NYHA II-IV, 17 of ischemic origin, 16 with idiopathic dilated cardiomyopathy) and 15 healthy controls (62.5±9.8 years) were examined. 13 patients were aspirin free and 20 patients were taking aspirin (100 mg/d). Serum IL-10 concentrations were measured using commercially available immunoassays. Patients with CHF showed significantly lower IL-10 concentrations as compared to controls (2.3+1.9 vs. 5.0+2.5 pg/mL, $p<0.001$). IL-10 serum concentration did not correlate with the NYHA-class. Aspirin therapy did not significantly influence serum levels of IL-10.
Conclusions: Our study demonstrates for the first time significantly reduced serum levels of IL-10 in patients with congestive heart failure. Since IL-10 is known as a potent anti-inflammatory cytokine, its decrease in CHF is an important component in the inflammatory response found in CHF.

1997 Platelets contribute to the inflammatory response in chronic heart failure via enhanced levels of CD154

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Background: Inflammation plays a contributory role in the pathogenesis of chronic heart failure (CHF). Previous data showed enhanced plasma levels of proinflammatory cytokines (i.e. TNF-alpha, IL-6) as well as persistent immune activation in patients with CHF. However, little is known about the role of CD154, an essential inflammatory mediator, in the pathophysiology of CHF. In intervention studies, blockade of CD154 significantly reduced inflammation in chronic inflammatory disease states such as rheumatoid arthritis and atherosclerosis. In addition, CD154 was identified on activated platelets, which is able to induce an inflammatory reaction within the vessel wall. In the current study, we focused on the expression of CD154 on platelets to further examine its inflammatory role in CHF.
Methods: We analysed the surface levels of CD154 on platelets in 33 patients with CHF of NYHA functional class II-IV (67.7+11.2 years, mean ejection fraction 20.9+7.0%, 17 of ischemic origin, 16 with idiopathic dilated cardiomyopathy) and 15 healthy controls (C, 62.5±9.8 y). 13 patients were aspirin free and 20 patients were taking aspirin (100 mg/d). Blood samples were drawn from a peripheral vein and immediately fixed with 1% paraformaldehyde. Another sample was centrifuged for preparation of platelet-rich plasma (PRP). Samples were thereafter stained with anti-CD154, anti-P-selectin and anti-CD61 (for identification of platelets). Platelets were analysed by flow cytometry.
Results: CHF patients showed significantly enhanced expression of platelet-bound CD154 and P-selectin as compared to healthy controls (CD154: 37.73+14.68 vs 9.35+5.65 mean fluorescence intensity [MFI], $p<0.001$; P-selectin: 5.19±1.79 vs 1.25+0.59 MFI, $p<0.001$). CD154 expression on platelets positively correlated with the increase in the NYHA-class. No significant correlation was detectable between the expression of CD154 and P-selectin in the study groups. Aspirin therapy did not significantly influence the expression of CD154 or P-selectin.
Conclusions: This first demonstration of enhanced levels of platelet-bound CD154 in patients with CHF suggests a contributory role of platelets to the inflammatory milieu found in CHF. Therefore, patients with CHF may benefit from pharmacological means (i.e. clopidogrel, statins), which interrupt the proatherogenic and proinflammatory CD40-CD154 pathway.

1998 Increased levels of proinflammatory cytokines correlate with a reduced expression of insulin-like growth factor-I in chronic heart failure

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Chronic heart failure (CHF) is associated with metabolic abnormalities leading to a progressive catabolic state. To assess the role of proinflammatory cytokines for the local expression of insulin-like growth factor-I (IGF-I) in this process, local levels of interleukin-1 beta (IL-1beta) and tumor necrosis factor alpha (TNFalpha) as well as IGF-I were analyzed in the skeletal muscle in addition to the determination of serum levels in a rat model of CHF.
Ligation of the left coronary artery (n=20) or sham operation (n=8) was performed in adult Wistar Kyoto rats (250g). After 12 weeks, all animals were assessed by echocardiography and cardiac catheterization for signs of CHF. Serum levels of IGF-I were measured by immunoassay and IL-1beta, IL-6 and TNFalpha concentrations assessed by ELISA. In quadriceps muscle, the expression of IGF-I, IGF-I receptor, IL-1beta and TNFalpha were assessed by RT-PCR and quantitative immunohistochemistry. Alterations in muscle fiber morphology were microscopically analyzed on tissue sections.
The expression of IGF-I significantly decreased in quadriceps muscle of animals with signs of CHF (0.47±0.07 versus 0.77±0.09 in Sham-OP; $p<0.05$). This reduction correlated with a decreased muscle fiber cross-sectional area ($r=0.62$; $p<0.01$) and inversely with the local expression of IL-1beta ($r=-0.49$; $p<0.05$). No significant differences in serum levels of IGF-I nor proinflammatory cytokines were found between the two groups.
The local expression of IGF-I is reduced in the presence of normal serum IGF-I levels in CHF. In addition to catabolic effects of proinflammatory cytokines, these findings are consistent with an involvement of altered local IGF-I levels in progressive skeletal muscle atrophy in CHF.

1999 Atrial fibrillation as an independant factor of increased circulating pro-inflammatory cytokines levels in heart failure

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Background: Proinflammatory cytokines play a pathogenic role in the development of congestive heart failure, and their circulating levels correlate with adverse outcome. Atrial fibrillation (AF) has been recognized as an independent factor of morbidity and mortality in these pts. Our study sought to investigate the relationship between chronic AF (>1 months) and circulating cytokine levels in pts with Idiopathic Dilated Cardiomyopathy (IDC).
Methods: We analyzed circulating levels of Tumor necrosis factor-a (TNF-a), and its soluble receptors sTNFr-1 and sTNFr- 2, Interleukine-1(IL-1) and -6 (IL-6) by immunobiological assay, in 92 pts, aged 59 ± 6 years, with IDC, angiographically proven, functional NYHA class II-III and Ejection Fraction (EF) 30.5±9.7%, in clinical stable condition during the last month. Seventy-two pts were in sinus rhythm (SR) and twenty in AF. A complete Echocardiographic study and cardiopulmonary exercise test with Naughton Protocol was performed in all pts, and maximal exercise duration and oxygen consumption at peak exercise (PVO2) were calculated.
Results: There was no significant difference between the two groups concerning age, left ventricular (LV) dimensions and volumes, LV Ejection Fraction and functional NYHA class, while left atrial (LA) dimensions were increased(46.2±5.8 vs 44±5.2 mm, p=0.05) in AF. Patients with AF had statistically significantly increased levels of IL-6 (6.2±3.2 vs 3.6±3.5 pg/ml, p=0.01), sTNFr1 (1.95±0.59vs 1.5±0.57pg/ml, p=0.01) and a trend of increased TNF-a (3.2 ±1.5 vs 2.6±1.1 pg/ml, p=0.07). Maximal exercise duration (548±283 vs 775±390 sec, p=0.03) and oxygen consumption at peak exercise(16.4±4.2 vs 18.1±3.2 ml/kgr/min, p=0.05) were also reduced in the AF patients group as compared to those in SR.
IL-6 was significantly correlated with AF (r=0.46, p=0.01), NYHA class (r=0.41, p=0.03), LVEF (r=-0.35, p=0.05), LA dimensions (r=0.38, p= 0.02) and RVEF (r=-0.39, p=0.05). Multivariate linear regression analysis showed that IL-6 (p=0.05) was independently associated with the presence of AF in these pts.
Conclusions: In idiopathic dilated cardiomyopathy, AF is an independent determinant of higher cytokine levels among pts with similar clinical and hemodynamic characteristics, supporting an increased proinflammatory status which may account for the reduced exercise performance in these patients.

2000 Influence of lipoproteins on cytokines and cytokine receptors in heart failure patients and the effect of short-term treatment with pravastatin

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Background: The observation that low total cholesterol predicted poor survival in patients with heart failure, has questioned the beneficial effect of lipid-lowering in this population. We undertook a study to assess the relation between lipoprotein concentrations and the levels of interleukin (IL)-6, tumor necrosis factor (TNF)-alpha and the soluble TNF-alpha receptors. In a subset, we investigated the effect of pravastatin on cytokine and TNF-alpha receptor concentrations.
Methods and Results: 71 patients with heart failure due to coronary artery disease (CAD, n=36) or idiopathic dilated cardiomyopathy (IDCM, n=35) participated in the study. Plasma concentrations of lipoproteins, IL-6, TNF-alpha, soluble TNF-a receptor 1 (sTNFR1) and 2 (sTNFR2) were measured. In 58 patients, measurements were repeated after 1 month treatment with pravastatin 40 mg. Total cholesterol/HDL-cholesterol (CHOL/HDL) correlated with levels of TNF-alpha (r=0.24, p<0.05), sTNFR1 (r=0.32, p=0.008) and sTNFR2 (r=0.37, p=0.002). In the CAD group, CHOL/HDL and triglycerides (TG) correlated with sTNFR2 (r=0.48, p=0.005 for CHOL/HDL, r=0.40, p=0.02 for TG). No relation was found between lipoproteins and cytokines or sTNF-alpha receptors for IDCM patients. Pravastatin induced a significant decline in IL-6 (p=0.01) and sTNFR2 (p= 0.008) in patients with the highest concentrations before treatment.
Conclusion: An atherogenic lipid profile favored the inflammatory process in patients with heart failure due to CAD, whereas no relation between lipoproteins and proinflammatory cytokines or TNF-alpha receptors was detected in case of IDCM. Pravastatin, administered during 1 month, did not adversely affect cytokine and sTNF-alpha receptor levels in these patients. On the contrary, in patients with CAD, IL-6 and sTNFR2 were significantly lowered.

CAN WE BUILD A NEW HEART FROM STEM CELLS?

2009 Non-cardiac cells in human transplanted hearts rebuild cardiomyocytes

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Stem cells able to differentiate into cardiomyocytes are discussed for cell replacement therapy to remodel damaged myocardium. A physiological or pathophysiological situation in which this phenomenon might be relevant is not known. Origin of cardiomyocytes in male patients having undergone sex-mismatched cardiac transplantation was studied to examine if cells containing a Y-chromosome body and therefore being of recipient origin are able to differentiate into cardiomyocytes.
Myocardial biopsies (n=21) were obtained from right ventricles of male patients (n=13) having undergone gender mismatched heart transplantation. Tissue from one nontransplanted male and myocardial biopsies from sex-matched heart transplanted patients served as controls. Cells from donor and recipient origin were identified by fluorescence in situ hybridization using probes specific for X- (DXZ1) and Y-chromosome (Y3.4) bodies on paraffin sections of the biopsies. The different cardiac cell types were identified using immunostaining procedures on the same tissue sections.
In 8 of 13 male recipients of female hearts cardiomyocytes of recipient origin were detected. In the positive biopsies, a mean (±SEM) of 0.18 ± 0.036 percent of the cardiomyocyte nuclei contained a Y-chromosome body. There was no detectable correlation to extent or number of rejection episodes, to time of transplantation or medical treatment regimen.
Cardiomyocyte regeneration in humans can occur by cells of non-cardiac origin, presumably bone marrow cells. This may lead to the development of new therapeutic strategies in the treatment of myocardial infarction, inflammatory heart disease or heart failure.

2010 Host cell-derived cardiomyocytes in sex-mismatch cardiac allografts

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Background: Mesenchymal stem cells are able to respond to tissue signals and differentiate into a phenotype characteristic of mature cells of that tissue. We sought to investigate whether adult human cardiomyocytes can be derived from recipient precursor cells in sex-mismatched cardiac allografts.
Methods ans Results: We studied four male patients who received hearts from female donors, and four female patients who received an allograft from a male donor. Four sex-matched transplant patients, two of each sex served as controls. Combined fluorescence in situ hybridization with probes specific for X- and Y-chromosomes and immunohistochemistry with alpha-actin was used to identify cardiac muscle cells four months and twelve months after transplantation. Slides were examined with a fluorescence microscope to detect the presence of male cells with one X and one Y signal in the nucleus, and female cells containing two X signals. Mature cardiomyocytes from the host (1 to 2%) were found in five endomyocardial biopsy specimens at four months, and in three specimens at twelve months. In addition, recipient cells negative for cytoplasmic alpha-actin were also identified (1 to 21% per slide). The number of infiltrating recipient cells was not associated with the degree of rejection of the sample or with the number of prior rejection episodes. Echocardiographic evaluation showed no improvement in cardiac performance in hearts from patients with more than 10% chimeric recipient cells.
Conclusions: Our data confirm the existence of mature cardiomyocytes derived from host cells, likely mesenchymal precursors, in the adult cardiac allograft in vivo.

2011 Transplantation of highly purified lentiviral transduced candidate stem cells from bone marrow in a porcine myocardial infarction model

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Introduction: Cell transplantation is a potential strategy to regenerate myocytes and improve function after myocardial infarction (MI). We transplanted highly purified autologous bone marrow (BM) derived gene marked candidate stem cells into infarcted myocardium to assess for improvement in myocardial function and myocyte regeneration.
Methods: Twelve young domestic swines underwent our study protocol. Nine pigs underwent iliac crest BM aspiration. BM cells were stained with Hoechst 33342 dye and sorted for side population "SP" cells by FACS. The SP cells were transfected with lentiviral vectors containing the green fluorescent protein (GFP) gene. All animals underwent left thoracotomy for coronary artery ligation 2 days after BM aspiration for SP injected pigs. The 2nd diagonal artery was ligated for 30min followed by reperfusion. Nine pigs were injected with autologous transduced SP cells with a 30 gauge tubuculin syringe. Control pigs (n=3) were injected with serum-free media without BM cells. Surviving animals were sacrificed at 4 weeks post-MI, and hearts removed for immunohistochemistry. Left ventricular functions were measured with Millar catheters and Sonometric crystals at baseline, immediate post-MI, and 4 weeks post-MI.
Results: Two BM injected pigs died 6 days post-MI, the remainder survived to 4 weeks. Quantity of sorted SP cells ranged from 15-64 thousand cells, with the exception of 1 pig (1.5 million cells). Control pigs had lower Emax immediately after ligation compared to baseline (2.83 vs 5.09, p=0.26); this was further reduced 4 weeks post-MI compared to baseline (1.36 vs 5.09, p=0.03). SP injected pigs had significantly reduced Emax immediately after ligation compared to baseline (2.11 vs 3.32, p=0.005), but returned to baseline level 4 weeks post-injection (3.38 vs 3.32, p=0.95). Similar trends were found for injected pigs with dP/dT+, dP/dT-, cardiac output, and stroke work. Preliminary histology of one pig which died at 6 days demonstrated positive anti-GFP stain in myocardium and capillary walls of border zone of the MI. Complete immunohistochemistry is pending.
Conclusions: Injection of autologous bone marrow derived gene marked SP cells into infarcted myocardium appeared to improve cardiac function measured at 4 weeks following transplantation. However, the small number of animals prevents definite conclusions. Support for injected cells contributing to myocard regeneration was obtained by detection of GFP-positive cells in border zone of MI at day 6 and completion of immunohistochemical analysis at 4 weeks post-MI is pending.

2012 Mobilization of endothelial progenitor cells during ischaemia

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The proportional contribution of endothelial progenitor cells (EPC) to postnatal neovascularization still remains to be clarified. In this respect, we observed a significant difference in angiogenic response between systemic and local treatment with nicotine. We investigated whether this is due to enhanced mobilization of EPCs by systemic nicotine treatment and related our findings to established factors like GM-CSF and statins.
Methods and Results: We employed a parabiotic model to identify EPC from reservoirs both inside and outside of the bone marrow. Male tie-2-LacZ FvB/N mice were connected to female wild type FvB/N mouse. Four weeks later, adjustment of blood cells between the animals had occurred. Hind limb ischemia was induced in the wild type mouse and animals were treated with nicotine, GM-CSF, cerivastatin or control. EPCs that incorporated into new or enlarging vessels during ischemia-induced revascularization were identified by co-localization for CD31 and LacZ. Non-bone-marrow-derived EPCs were identified by a reverse bone marrow transplantation (rBMT) model: male tie-2-LacZ FvB/N mice were transplanted with wild type FvB/N bone marrow and connected to female wild type FvB/N mice. Vessel density was significantly higher in animals treated with nicotine, GM-CSF, or cerivastatin as compared to control ($P<0.001$). Incorporation of EPCs in the control group was rare (1.6% of the vessels). In the nicotine group, however, EPCs were detected in 9.3% of the vessels ($P<0.001$; GM-CSF 21.5%, Cerivastatin 15.5%). In the rBMT model, still 1.0% and 5.1% of the vessels in the control and the nicotine group, respectively, contained EPCs. In mice with ischemic hind limbs, nicotine had stimulated the number of CD34/Flk-1-positive cells in bone marrow and spleen with a peak at 7 days (2.3- and 1.9-fold increase, respectively; $P<0.01$). In vitro studies demonstrated that nicotine induced expression of integrins (alpha-v, alpha-5, beta-1) on isolated EPCs.
Conclusions: We demonstrate that the relative contribution of EPCs to ischemia-induced angiogenesis in control animals is low. However, EPC incorporaton can be enhanced by systemic administration of nicotine, GM-CSF, and cerivastatin, respectively. Further, we show that EPCs can be mobilized from other sources than the bone marrow.

2013 Smooth muscle cells in transplant atherosclerotic lesions are originated from recipients, but not bone marrow progenitor cells

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Smooth muscle cell (SMC) accumulation in the intima of vessels is a key event in the pathogenesis of transplant atherosclerosis. Traditional hypothesis that SMCs in the lesion are derived from the media of the donor vessel is challenged by recent observations, but their origins are not well established. Herein, we use a simplified model of artery allografts in transgenic mice to definitely identify the source of SMCs in transplant atherosclerosis. Aortic segments donated by BALB/c mice allografted to ROSA26 mice expressing beta-galactosidase (gal) in all tissues showed that neointimal cells derived exclusively from host cells. It was also demonstrated that SMCs of neointimal and atherosclerotic lesions in vessels allografted to mice expressing beta-gal only in SMCs (SM-LacZ) or to apoE-deficient/SM-LacZ mice were originated from recipient, but not donor vessels. Interestingly, bone-marrow transplantation of SM-LacZ beta-gal expressing cells into aortic allograft recipients revealed completely X-gal negative staining of neointimal and atherosclerotic lesions, although a population of X-gal+ cells in allografts in mice having ROSA26 beta-gal expressing marrow cells. When bone marrow cells from both ROSA26 and SM-LacZ mice were cultivated in vitro and stimulated with PDGF-BB, alpha-actin and beta-gal double-positive cells were identified, suggesting that bone marrow cells have an ability to differentiate into SMCs. Thus, we provide the definite evidence that SMCs of neointimal and atherosclerotic lesions in allografts are derived from recipients and that circulating and non-bone marrow-derived progenitor cells might be the source of SMCs in atherosclerotic lesions.

GENE THERAPY IN CORONARY AND MYOCARDIAL DISEASE

2021 Safety of catheter-based local intracoronary VEGF gene transfer in the treatment of chronic myocardial ischaemia and restenosis; KAT-trial

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Catheter-based intravascular gene transfer is a potential treatment for ischemic heart diseases. The objective of this study was to evaluate safety of local catheter-mediated VEGF -plasmid/liposome and VEGF-adenovirus gene therapy in patients with severe chronic ischemic heart disease.
Methods: 103 patients with coronary heart disease (NYHA II-IV) were recruited in this randomized, placebo-controlled, double-blinded phase II study. Gene transfer to coronary arteries was performed after coronary angioplasty (PTCA) with a perfusion-infusion catheter. Thirty seven patients received 2x10E10 pfu VEGF-adenovirus (VEGF-Adv), 28 patients VEGF -plasmid-liposome (VEGF-P/L; 2000 μg of DNA with 2000 μl of DOTMA:DOPE (1:1 w/w) liposome) and 38 control patients received Ringer lactate. Gene transfer was performed during 10 min injection time at the site of PTCA. Safety laboratory parameters and clinical symptoms were followed for 2 days at the hospital and during 6 months follow-up time. A questionnaire survey was performed 14 to 47 months after the gene transfer to evaluate late safety outcome of the treatment.
Results: Gene transfer to coronary arteries was feasible and well tolerated. Patients did not need additional medication during gene transfer and none of the patients developed hypotension during hospital stay. No major gene transfer–related side effects were detected during the follow-up. One death occurred in VEGF-Adv group 20 months after procedure and was considered unrelated to gene transfer. Two new cancers were diagnosed during long-term follow-up in VEGF-P/L group. Although increases in serum CRP, LDH, IL-6 and anti-Adv-antibody levels were seen in VEGF-Adv group, no significant abnormalities in other laboratory parameters were detected. Fever was seen in all study groups, but was most frequent in VEGF-Adv group (51% vs. 39% vs. 3%; VEGF-Adv vs. VEGF-P/L vs. placebo, respectively).
Conclusions: Catheter-based local gene transfer with either VEGF-P/L or VEGF-Adv during PTCA shows that: (i) intracoronary gene transfer can be performed safely, (ii) some inflammatory responses are present in VEGF-Adv group, (iii) no increase was detected in the incidence of new cancers or other serious adverse effects. Angioplasty combined with VEGF gene therapy is potentially applicable for the treatment of ischemic heart diseases.

2022 Efficient endothelial gene transfer with preserved vascular integrity by ultrasound-enhanced destruction of plasmid-loaded albumin microbubbles

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Local vascular gene therapy has enormous potential for the treatment of vascular disease. However, previous techniques used for vascular gene therapy were hampered by the destruction of the endothelial cell layer. Therefore we investigated whether diagnostic ultrasound-mediated destruction of plasmid-loaded albumin microbubbles is a feasible and efficient technique for local vascular gene delivery without impairment of the endothelial cell layer.

Methods and Results: Gas-filled microbubbles (3.0±1.2 μm) were created by sonication of 5% human albumin in the presence of plasmid DNA encoding for LacZ. Porcine coronary arteries were perfused (flow rate 2 ml/min) with DNA-loaded albumin microbubbles in vitro, exposed to diagnostic ultrasound (2.2 MHz, mechanical index 1.2, frame rate 172.9 frames/sec, 5 seconds) and further incubated for 24 hours. Detection of the β-galactosidase in LacZ transfected vessels revealed intense blue staining predominantly of the endothelial cells (>90%), while vessels perfused with an empty vector but otherwise treated identically showed no staining. Trypan blue staining of the endothelium and measurement of LDH activity in the perfusate excluded a cytotoxic effect of the treatment on the endothelial cell layer. Microscopy revealed no histologically detectable alterations of the vessel wall. Bradykinin-induced endothelium-dependent relaxation was similar in untreated control vessels and vessels exposed to microbubbles and ultrasound (pD2 (-logEC50): 9.28±0.07 vs. 9.87±1.35, p=0.68, n=4).

Conclusion: Our study demonstrates efficient gene transfer to the endothelial cell layer of conductance arteries by ultrasound-mediated destruction of albumin-coated microbubbles loaded with naked plasmid DNA. Despite efficient transgene expression, the structural and functional integrity of the transfected endothelial cell layer was well preserved after ultrasound treatment. Thus, this method appears to be ideally suited for gene delivery to the endothelial cell layer of conductance vessels.

2023 Antagonism of the renin angiotensin system counteracts cardiac angiogenic VEGF gene therapy

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Background: Vascular endothelial growth factor (VEGF) is a potent endothelial cell specific mitogen with a proven efficacy to induce angiogenesis in variety of animal models. Angiotensin converting enzyme inhibitor and angiotensin-2 antagonists are common drugs used in cardiovascular diseases, which may counteract angiogenesis.

Aim: To test the hypothesis that angiotensin converting enzyme inhibition or angiotensin-2 antagonism may counteract cardiac phVEGF- A165 gene therapy for angiogenesis.

Methods: C57Bl/6, 6-8 week old mice were given a single intramyocardial injection of phVEGF-A165 (5mgm) via a thoracotomy (n=16). From day 1, one group (n=8) of mice received daily subcutaneous injection of enalapril (30mgm/kg) and a second group (n=8) got candesartan (20mgm/kg) for 10 consecutive days. Two separate groups of mice (n=7) received intramyocardial injection of normal saline or phVEGF-A165 alone as control. On day 10, hearts were harvested for cryosection and capillary count done by immunohistochemistry. With similar design, four groups (n=6 each) of mice were taken for determination of tissue expression of VEGF protein after 24 hours.

Results: Gene transfer of phVEGF- A165 alone increased myocardial capillary density 1.16 fold compared to control (602±57 vs 520± 31/sq. mm, P< 0.005). In candesartan treated mice phVEGF- A165 did not induce any angiogenesis and capillary density was in fact lower than in controls treated with saline (484±14 vs.520±31/sq. mm, P<0.001). Enalapril induced a tendency (P<0.10) to inhibition of phVEGF- A165 induced angiogenesis.VEGF-A165 immunoassay showed decreased expression of phVEGF-A165 in hearts treated with enalapril or candesartan compared to control (candesartan: 20±23 pg/ml, enalapril: 25±35 pg/ml vs. phVEGF- A165 alone 105±68 pg/ml, P<0.001).

Conclusions: Candesartan inhibits phVEGF-A165 induced cardiac angiogenesis while enalapril showed a tendency to inhibition. Also, candesartan inhibited endogenous capillarisation. In the expression chain from gene to capillary growth the angiotensin II inhibition exerts its effect at or before the formation of the VEGF protein.

2024 Lentiviral vectors efficiently transduce genes into human coronary endothelial and smooth muscle cells in vitro and into rat arteries in vivo

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Retroviral vectors provide a potential for permanent gene modifications of target cells as a result of chromosomal integration. However, murine oncoretroviral vectors do not efficiently transduce genes into growth-arrested endothelial cells (EC) in vitro and EC in normal arteries in vivo, which have very low proliferation rates. Among retroviral vectors, lentiviral vectors are unique in that they transduce genes both into dividing and into nondividing cells.

Methods: Vesicular stomatitis virus-pseudotyped, multiply attenuated (deletions of nef, vif, vpr, vpu, env, tat) and self-inactivating (SIN; large deletion in the U3 region of the 3' long terminal repeat) vectors derived from human immunodeficiency virus (HIV)-1 were produced using a four-plasmid conditional packaging system. Cis-acting sequences including the woodchuck hepatitis virus posttranscriptional regulatory element and the central polypurine tract (cPPT) sequence from HIV-1 pol that enhances nuclear translocation were inserted into the vectors. The EGFP reporter gene was expressed under the control of various promoters including the cytomegalovirus (CMV), elongation factor-1alpha (EF-1alpha), phosphoglycerate kinase, and the endothelium-specific angiopoietin Tie-2 receptor promoter. Gene transfer was studied in human umbilical vein EC (HUVEC), human coronary artery EC (HCAEC) and human coronary artery smooth muscle cells (HCASMC) in vitro (by FACS), and in rat carotid arteries in vivo (by fluorescence microscopy).

Results: SIN vectors at a multiplicity of infection (MOI) of 3 transduced the EGFP gene into ~95% of HUVEC and HCAEC. Similar transduction rates were achieved in HCASMC with a MOI of 30. Gene transfer efficiency in HCAEC and HCASMC was 5 to 10-fold higher as compared to adenoviral vectors. Highest EGFP expression levels were achieved with the CMV and EF-1alpha promoters in both cell types, while the Tie-2 promoter also achieved high EGFP expression levels in HCAEC. SIN vectors at a MOI of 10 transduced ~20%, 35% and 60% of HCAEC after 30, 60 and 120 minutes, respectively. In vitro EGFP expression in HCAEC lasted for >4 weeks, whereas adenoviral expression was lost. SIN vectors transduced ~5% EC in rat arteries in vivo.

Conclusions: Multiply attenuated, self-inactivating lentiviral vectors transduce genes into human EC and SMC in vitro. The efficiency of gene transfer is higher than with adenoviral vectors. These vectors also efficiently transduce genes into rat arterial endothelium in vivo. Lentiviral vectors are a useful system for vascular gene delivery both in vitro and in vivo.

2025 Infarct size limitation by gene transfer of baculoviral P35 into rat myocardium

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Apoptosis plays a pivotal role in determining the extent of injury during myocardial infarction. Inhibition of apoptosis has been shown to protect myocardium from damage during ischemia and reperfusion. The aim of this study was to determine whether gene transfer of baculoviral protein p35, a potent inhibitor of apoptosis, into myocardium could limit infarct size. Methods: Male Wistar rats were directly injected into the left anterior ventricular wall with adenoviral vector encoding baculoviral p35. 72 hours later hearts were excised and mounted on a Langendorff apparatus and perfused. The left anterior descending artery was ligated for 30 minutes and reperfused for 2 hours. Area at risk and infarct size were determined by staining with bromophenolblue and triphenoltetrazoliumchloride (TTC), respectively. Apoptosis was assessed by staining cryosections for DNA-strand breaks (TUNEL-assay) and caspase-3 activity. Results: Infarct size was significantly reduced in animals treated with p35 (59±3% reduction, p<0.05), whereas no reduction was seen when only control vector was injected. TUNEL-positive nuclei and caspase-3 activity was diminished significantly only in animals treated with p35. Conclusion: Gene transfer of the baculoviral protein p35 into the left ventricular myocardium reduces apoptosis and limits infarct size after regional ischemia and reperfusion.

2026 VEGF expression in human macrophages is NFkB-dependent: studies using adenoviral gene transfer

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Background Vascular endothelial growth factor (VEGF) is a multifunctional cytokine, as it can induce endothelial cell proliferation and migration, inhibit apoptosis and regulate physiological and pathological angiogenesis. VEGF is abundantly found in human atherosclerotic plaques. Although therapeutic angiogenesis via VEGF delivery represents a promising treatment for ischemic heart disease, it has been recently suggested that administration of VEGF enhances atherosclerotic plaque progression in experimental models. The mechanisms involved in VEGF production are still under investigation. The aim of our study was to dissect the intracellular signalling pathways involved in VEGF production in primary human macrophages, one of the major cell type expressing VEGF in atherosclerotic plaques.

Methods Elutriation-enriched monocytes were obtained from peripheral blood mononuclear cells from single donor plateletpheresis residues, and cultured in the presence of macrophage-colony stimulating factor for differentiation to macrophage-like phenotype. Macrophage were infected with adenoviral vectors encoding I kappa B alpha, the natural inhibitor of NFkB nuclear translocation (AdvIkBa), a kinase negative mutant of the upstream kinase IKK2, essential to NFkB activation (AdvIKK2dn), or without insert as control (Adv0). A multiplicity of infection of 100:1, at which the efficiency of infection was >95%, was used. After infection cells were stimulated with Lipopolysaccharide (LPS) or co-cultured with mouse fibroblasts transfected with a plasmid expressing CD40 ligand (CD40L). Alternatively cells were stimulated with recombinant soluble human CD40L. VEGF was measured by ELISA.

Results We observed that LPS-induced production of VEGF by macrophages was completely inhibited (>95%) following adenoviral transfer of IkBa. Engagement of CD40 on macrophages induces VEGF release at levels comparable to those obtained with LPS. We observed strong inhibition of the CD40L-induced VEGF production in macrophages following infection with AdvIkBa. However, expression of IKK2dn in macrophages decreased both LPS- and CD40L- induced VEGF production by approximately 50%, suggesting that in addition to IKK2 other kinases may be involved in NFkB activation.

Conclusions CD40-CD40L interaction leads to VEGF induction, suggesting that ligation of CD40 on macrophages could potentially promote expression of VEGF in the human atherosclerotic plaque. Moreover, this is, to our knowledge the first report that NFkB activation is required for LPS-induced and CD40L induced VEGF production in primary human macrophages.

EUROPEAN SOCIETY OF CARDIOLOGY LECTURE ON BASIC SCIENCES

2032 The sarcolemmal Na^+/Ca^{2+} exchanger critically contributes to hydroxyl radical-induced injury in rabbit ventricular myocytes

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Background: Large amounts of reactive oxygen species (ROS) occur in the myocardium during reperfusion after ischemia and play a fundamental role in the development of reperfusion injury. Isolated cardiac myocytes, when exposed to ROS, undergo hypercontracture in association with cytosolic calcium overload and eventually cell death. We investigated the contribution of Ca^{2+} entry via the Ca^{2+}-uptake mode of the sarcolemmal Na^+/Ca^{2+} exchanger (NCX), which is an important regulator of Ca^{2+} homeostasis in cardiac myocytes, to this ROS-induced Ca^{2+} overload.

Methods: Rabbit isolated ventricular myocytes after 24h of culture were transiently exposed to hydroxyl radical (*OH) during an interval of 4min by addition of 100 μmol/L H2O2 to the superfusate (Krebs-Henseleit solution, $[Ca^{2+}]_o$ 1.75 mmol/L) in the presence of Fe3+/NTA (100 μmol/L, 200 μmol/L), which generates *OH via a Fenton reaction. Over a period of 30 minutes cell shape was monitored and the fraction of cells undergoing hypercontracture (Fhyper) was assessed. Following *OH exposure, Fhyper increases with time in a sigmoidal relationship that can be fitted with a Boltzman equation, from which the fraction of non-responder cells (Fnr) can be derived as a measure of susceptibility to radical-induced damage.

Results: *OH exposure under control conditions caused cells to hypercontract with Fnr = 0.29 ± 0.07. Preincubation with 100μmol/L melatonin, a radical scavenger highly specific for *OH, resulted in significant protection against radical-induced hypercontracture (Fnr = 0.69 ± 0.11; P = 0.001), confirming that hydroxyl radical represents the predominant ROS generated under these experimental conditions. Pretreatment of cells with 5 μmol/L KB-R7943, which is considered to specifically inhibit NCX-mediated Ca^{2+}-entry, also afforded significant protection against radical-induced hypercontracture by enhancing Fnr (0.29 ± 0.14 vs. 0.62 ± 0.14; P < 0.038), suggesting an essential contribution of NCX in calcium overload.

Conclusions: Ca^{2+}-entry via NCX is a critical mediator of *OH-induced injury in rabbit ventricular cardiomyocytes. Since NCX expression is upregulated in the failing heart, this molecule may represent a promising drug target to prevent ROS-induced damage in heart failure and ischemia/reperfusion.

2033 Evidence for active inflammation and interstitial remodelling in the hibernating human myocardium

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Myocardial hibernation is associated with structural myocardial changes, which involve both the cardiomyocytes and the cardiac interstitium. We hypothesized that myocardial hibernation may be associated with an active inflammatory process leading to leukocyte recruitment in the cardiac interstitium. We obtained transmural myocardial biopsies guided by transesophageal echocardiography, from patients with ischemic ventricular dysfunction undergoing coronary bypass surgery. Among the 28 biopsied segments included in the study, 23 showed evidence of systolic dysfunction. The majority of dysfunctional segments (85.7%) were viable (201Tl uptake >60%). The samples were stained with markers for mast cells, mature resident macrophages and the monoclonal antibody Mac387, which labels newly recruited myeloid cells. Dysfunctional segments showed more extensive fibrosis and higher macrophage density than normal segments. Among the 23 dysfunctional segments, 12 recovered function as assessed with echocardiograms 3 months after revascularization. Segments with postoperative functional recovery had comparable macrophage and mast cell density with those showing persistent dysfunction. However, biopsied segments which subsequently recovered function contained significantly higher numbers of newly recruited Mac387 positive leukocytes (18.7±3.1 cells/mm^2, n=12 vs. 8.6±0.9 cells/mm^2, n=11 p=0.009). In addition, Monocyte Chemotactic Protein (MCP)-1, a potent mononuclear cell chemoattractant, was predominantly expressed in segments with recovery of function. Interstitial deposition of the matricellular protein tenascin, a marker of active remodeling, was higher in hibernating segments than in segments with persistent dysfunction (p<0.05), suggesting an active continuous fibrotic process. Myocardial hibernation is associated with an inflammatory response leading to active leukocyte recruitment. Dysfunctional myocardial segments, which show an active inflammatory reaction have a greater potential for recovery of function after revascularization. We postulate that revascularization may promote resolution of the ongoing inflammation, preventing further tissue injury and fibrosis.

2034 Beneficial effects of pre-infarction angina on the myocardial infarct size, myocardial viability, and functional recovery in reperfused Acute Myocardial Infarction

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Purpose: Pre-infarction angina (PIA) may limit infarct size, but the effects of PIA on myocardial viability and long-term functional recovery are not well clarified. The aim of this study was to determine the effects of PIA on the infarct size assessed by nuclear perfusion imaging, myocardial functional reserve by low-dose dobutamine echocardiography (LDDE) and long-term functional recovery of the asynergic area in patients who underwent immediate PTCA following AMI.

Methods: Forty-six patients with AMI underwent immediate PTCA (mean age = 63 yrs old). PIA was defined as positive when typical chest pain occurred in 48 hours before AMI. Resting 201-Tl or 99m-Tc MIBI-SPECT was performed at 7~14 days after AMI, and the extent and severity score were obtained. LDDE (5~10 mcg/kg/min) was performed to detect myocardial viability, and wall motion score was obtained. Follow-up echocardiography was repeated 6 month later to detect regional functional recovery of the infarct area.

Results: Thirty of 46 patients (65%) had PIA. Wall motion score and defect score of SPECT were significantly lower in patients with PIA than in those without PIA (mean = 6.8 vs. 9.0 points, $p<0.05$, mean = 7.4 vs. 12.4 points, $p<0.01$, respectively). The number of patients with long-term functional recovery and myocardial viability determined by LDDE were higher in PIA than in those without PIA (63% vs. 31%, 57% vs. 25%, respectively, $p < 005$). The effects of PIA on functional recovery and myocardial viability determined by LDDE were more evident in patients in whom coronary reperfusion occurred within 6 hrs after acute myocardial infarction (86% vs. 22%, 79% vs. 22%, respectively, $p< 0.01$). These beneficial effects of PIA were unclear in patients with coronary reperfusion time greater than 6 hrs. The patients of PIA without regional functional recovery in spite coronary reperfusion within 6 hrs showed re-occlusion of the infarct-related arteries.

Conclusion: PIA induced smaller infarct size, greater myocardial viability and better long-term functional recovery of the infarct area in patients with AMI who underwent immediate PTCA. These beneficial effects are evident when coronary reperfusion occurred in 6 hrs after acute myocardial infarction, but they are not clear after 6 hrs.

NEW CARDIAC MARKERS

2035 The predictive value of soluble P-selectin T in patients with chest pain and a normal or non-diagnostic electrocardiogram

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Background: The glycoprotein P-Selectin is rapidly translocated from a-granules of platelets and Weibel-Palade bodies of endothelial cells to the cell surface on stimulation. Endothelial cell and platelet activation is also associated with a rise of blood concentration of a soluble form of this protein. Surface bound P-Selectin is suggested to be subsequently shed into the circulation. As activation of endothelial cells does not produce raised levels of soluble P-Selectin, platelets are thought to be the major source.

Raised levels of blood P-Selectin have been reported to be associated with cardiovascular events on admission.

Objective: The aim of this study was to assess the diagnostic value of soluble P-Selectin for myocardial infarction, and the prognostic value of P-Selectin for cardiovascular events in patients with chest pain and a normal or non-diagnostic electrocardiogram.

Patients and methods: We determined the predictive value of soluble P-Selectin on admission for detecting acute myocardial infarction (AMI: discharge diagnosis, Cardiac Troponin T >0,01 mg/l) or acute coronary syndromes (ACS: AMI or unstable angina) in 219 patients with chest pain of less than six hours duration and a normal or non-diagnostic electrocardiogram. Controls were patients without any cardiac event on admission or at 6 month follow-up. Analysis was performed using a Pearson Chi squared test. Cut-off level for soluble P-Selectin as reported in literature was 139 mg/l.

Results: Table 1 shows a 2 x 2 frequency table of occurrence of AMI and soluble P-Selectin level on admission.

Table 2 shows a 2 x 2 frequency table of occurrence of ACS and soluble P-Selectin level on admission.

Conclusion: In contrast to previous results, we found that in patients with chest pain of less than six hours duration and a normal or non-diagnostic electrocardiogram, soluble P-Selectin was unable to distinguish between patients with or without an acute coronary syndrome.

Table 1

	AMI	No event	Total
Sol. P-Selectin≥139 mg/l	11	25	36
Sol. P-Selectin<139 mg/l	50	107	157
Total	61	132	193

chi square = 0,023; p=0,881

Table 2

	ACS	No event	Total
Sol. P-Selectin≥139 mg/l	18	25	43
Sol. P-Selectin<139 mg/l	69	107	176
Total	87	132	219

chi square = 0,102; p=0,750

2036 Prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes

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N-terminal pro-BNP (BNP) is a neurohormone precursor synthesized predominantly in ventricular myocardium. Although the circulating level of BNP has been shown to provide independent prognostic information in patients with transmural myocardial infarction, few data are available for patients with acute coronary syndromes in the absence of ST-segment elevation.

Methods: We measured BNP in plasma samples obtained a mean (±SD) of 8.5±2.6 hours after the onset of ischemic symptoms in 467 patients from the PRISM study.

Results: The baseline levels of BNP correlated with the risk of death and myocardial infarction at 30 days. The unadjusted rate of death increased in a stepwise fashion among patients in increasing quartiles of baseline BNP($P<0.001$). This association remained significant in subgroups of patients who had myocardial infarction without ST-segment elevation ($P<0.01$) and patients who had unstable angina ($P<0.01$). The adjusted hazard ratio for death and myocardial infarction in the second, third, and fourth quartiles of BNP were 3.1 (95% CI 1.1 to 12.0), 2.9 (95% CI 1.3 to 10.5), and 4.5 (95% CI 1.5 to 12.3). The level of BNP was also associated with the risk of recurrent angina at 30 days ($P<0.001$).

Conclusions: A baseline measurement of BNP, obtained within 12 hours after the onset of ischemic symptoms, provides indpendent predictive information for use in risk stratification across the spectrum of acute coronary syndromes.

2037 Early treatment with statins and selective COX-2 inhibitor decreases CRP in patients with unstable angina undergoing catheterization

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Background: Elevated levels of C-reactive protein (CRP) in patients with unstable angina are associated with an increased risk of adverse cardiac events. We proved that there was more pronounced decrease of inflammatory markers in patients with unstable angina after combination of statin therapy and COX-2 inhibitor initiated immediately after percutaneous coronary intervention (PCI). The aim of this study was to assess if short period (3 days) of high dose statin therapy alone or in combination with COX-2 inhibitors administered before intervention could prevent further CRP elevation usually observed immediately after procedure.

Methods: 60 consecutive patients with unstable angina (II B,III B according to Braunwald) were studied 37 patients with CRP> 3 mg/l at baseline were randomized to three groups: gr. A received placebo, gr. B received 80 mg of atorvastatin, gr. C atorvastatin 80 mg and rofecoxib 25 mg. All patients received aspirin and ticlopidine before intervention and were scheduled to interventional procedure on 3-rd day. The levels of CRP were measured at baseline, day 3 and 48 hours after catheterization.

Results: Median CRP levels in group B were lower after 3 day of aggressive anti inflammatory treatment in comparison to placebo group. More pronounced decreased was observed in group C. The increase of CRP after angiography/PCI was also reduced in treated groups (see table). No adverse effects of tested medication (including thrombotic complications after COX-2 administration) were recorded.

Median CRP value

	A (mmol/l)	B (mmol/l)	C (mmol/l)
Baseline	4,00	4,26	7,71
Day 3	5,30	2,21	1,91
48 h after intervention	25,00	7,77	12,20

Conclusions: The combination of statins with COX-2 inhibitor administered before invasive treatment in patients with unstable angina is effective in lowering CRP levels in very short period of time. Attenuation of exaggerated inflammatory response before and during PCI could be crucial in reducing adverse cardiac events in these patients at follow-up.

2038 Ischaemia modified albumin (IMA™): a marker of ischaemia in patients presenting to the Emergency Department (ED) with cardiac chest pain

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Purpose: Biochemical markers exist which allow the diagnosis of myocardial cell death (necrosis). However, no markers are available in the clinical setting that can accurately detect myocardial ischaemia that develops before or in the absence of cell necrosis. We used the Albumin Cobalt Binding (ACB™) Test to detect IMA as a marker of myocardial ischaemia in patients with acute chest pain. This test is based on the fact that exposure of circulating albumin to ischaemic myocardial tissue modifies the N-terminus of albumin such that its binding capacity to exogenous cobalt is reduced.
Methods: We prospectively measured IMA (by a rapid ACB assay) on 131 consecutive patients, 90 male, and 41 female, mean age 61 ± 12 years, attending our ED with acute chest pain suggestive of acute coronary syndrome (ACS). Patients underwent 12 lead ECG, creatinine kinase, and troponin T measurements at study entry. We compared discharge diagnosis with the admission IMA value. A final diagnosis of ACS or non ischaemic pain (NICP) was made by the treating physician on the basis of clinical symptoms, ECG changes, CK and cTnT levels and angiographic results, blinded to the IMA value.
Results: Final diagnosis was NICP in 44 patients (27 male, 17 female, mean age 56 ±15 years) and myocardial ischaemia in 87 (63 male, 24 female, mean age 63 ±10 years). Ischaemia was associated with typical transient ST changes in 28 patients (21%) and by ECG T wave inversion > 2mm in 5 patients (4%). 37 (28%) had angiography with > 70% stenosis in addition to chest pain and/or ST segment changes. Patients with ischaemic chest pain had a significantly higher mean IMA value (97.8 U/mL ±13.8) compared to patients with NICP (87.58 U/mL ±13.0), $p<0.005$. Patients with IMA >93.4 U/mL (the median of the overall IMA distribution) had a relative risk (RR) of 3.34 [95% Confidence Interval (CI) of 1.55 to 7.19] to have ischaemic heart disease compared to those with IMA <93.4 U/mL. ECG ST deviation as a predictor of ischaemic heart disease yielded a RR of 1.74 (95% CI 1.47-2.06).
Conclusions: This study showed that in patients with chest pain IMA is a sensitive marker of ischaemia. It compared favorably to the presentation ECG for predicting risk of ischemic heart disease and therefore IMA may be a useful practical tool to risk stratify patients presenting to the ED with acute chest pain.

2039 Expression of macrophage migration inhibitory factor, a pro-inflammatory cytokine, in atherosclerosis and acute myocardial infarction

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Background: Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that involves in the regulation of inflammatory and immune responses by recruiting and localizing inflammatory cells to the diseased areas. In cardiovascular system, MIF might be involved in the pathogenesis of atherosclerosis where inflammatory cells are aggregated; and macrophage and T-cell-mediated myocyte damage in acute myocardial infarction (AMI). This study investigated if MIF is actively involved in these conditions.
Methods: In human study, blood was taken from 128 patients with coronary artery disease (37 with AMI) and 31 normal controls for MIF levels. Human coronary plaques were obtained from 11 patients during percutaneous coronary intervention (PCI), and from 7 normal and 5 atherosclerotic coronary arteries at postmortem. In animal study, AMI was induced by ligating the left anterior decending coronary arteries of the 10-week Sprague-Dawley rats. They were killed at 3 hr, 6 hr, 1 day, 3 days and 7 days. The expression of MIF was examined by RT-PCR, in-situ hybridization, immunohistochemistry, Western blot and ELIZA. The macrophage infiltration was also detected by anti-CD68 antibody.
Results: In atherosclerotic coronary plaques, MIF expression was observed in 10 out of 11 cases and mainly localized in the fibroblasts. In post-mortem atherosclerotic coronary arteries, stronger MIF expression was observed in all cases and localized in both the plaques and smooth muscle cell layer of tunica media, but not in normal controls. In rats with AMI, MIF mRNA ($p<0.001$) and protein ($p<0.05$) were expressed early at the peri-infarct zone of the left ventricle, and to a lesser extent in the myocytes of non-infarct septum and right ventricle. Macrophage infiltrated into the infarct zone from day 1 ($p<0.01$) and progressively increased over the 2-week course ($p<0.01$). The plasma levels of MIF in patients with AMI were significantly elevated 2-3 folds during day 1 (3114±789 vs 633±130 pg/mL, $p<0.001$) and day 2 (2323±565 vs 626±129 pg/mL, $p<0.001$) when compared with controls, but was not seen in patients with angina or underwent PCI.
Conclusion: In human atherosclerosis, up-regulation of MIF in the plaque and smooth muscle cells may play a role in macrophage adhesion and disease progression. MIF is also expressed during AMI, and may act as a modulator of inflammatory-mediated myocyte damage.

2040 Elevation of interleukin-15 serum levels in patients with acute coronary syndrome

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Several chemokines, such as interleukin-6 and TNF-alpha have been investigated as a marker for the inflammatory response during acute coronary syndromes. The presence of interleukin-15 (IL-15) has recently been demonstrated in human atherosclerotic plaques, suggesting a potential role in the pathogenesis of coronary artery disease. The underlying prospective study was designed to evaluate the role of IL-15 in patients (pts) with acute coronary syndrome.
4 patient (pts) groups were investigated: Healthy subjcts, in which coronary artery disease could be excluded by coronary angiography (Control), pts with angiographically documented stable angina (CAD), and pts with acute coronary syndrome, either with (AMI) or without (ACS) ST-elevation in the ECG. Pts with more than 2-fold elevation of the creatine-kinase above normal (>180 U/l) were defined as AMI. Pts with coexisting diseases other than hypertension or diabetes were excluded from the study. Serum chemokines were measured during the first 24 and 72 h (ACS or AMI) by ultra-sensitive ELISAs. IL-15 serum levels ranged between 1.8 and 8.0 pg/ml in pts with ACS or AMI, compared to 0.6 to 2.5 pg/ml in pts with CAD. IL-15 levels in pts with ACS or AMI were exclusively above the 75% percentile of the control or CAD group. IL-15 serum levels in the AMI group correlated well with IL-6 ($p=0.0051$) and IL-8 ($p=0.0117$) serum levels, which was not the case for the ACS group. There was no difference in IL-15 between the Control and Stable CAD group (see table).

Chemokine serum levels [pg/ml]

mean (± SEM)	Control (n=41)	CAD (n=40)	ACS (n=12)	AMI (n=12)
TNF-alpha	1.50 (0.15)	1.87 (0.12) NS	4.59 (1.04) #	3.94 (0.74) #
IL-6	0.80 (0.18)	0.82 (0.23) NS	24.08 (13.32) NS	77.04 (44.64) #
IL-8	14.66 (1.15)	15.65 (0.90) NS	75.05 (48.90) *	33.78 (10.16) NS
IL-15	1.50 (0.07)	1.43 (0.07) NS	2.95 (0.21) #	3.18 (0.62) #

NS not significant, *$p<0.05$, #$p<0.001$ (compared to Control). Maximum chemokine levels from the first 72h were used in ACS and AMI pts.

Conclusion: Serum levels of IL-15 were elevated only in pts with ACS or AMI, not with stable angina, indicating a possible role in the inflammatory response of the vessel wall during plaque rupture. In this preliminary and therefore small cohort, IL-15 seems to justify its anticipated adverse role in the vessel wall biology.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN ACUTE MYOCARDIAL INFARCTION

2041 Pre-hospital infarction angioplasty triage (PHIAT): a considerable reduction in ischaemic time

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Background: Time from onset of symptoms to reperfusion therapy is of paramount importance for clinical outcome in patients (pts) with acute myocardial infarction (AMI). When considering primary PTCA, pre-hospital identification of pts with large AMI may result in a reduction of ischemic time by transporting them directly to a PTCA centre.
Methods: From pts identified in the ambulance as having AMI data on time intervals were registered. Transportation distances from the patient's home to the nearest hospital were calculated using postal codes.
Results: From November 1998 to December 2000, 254 pts were identified in the ambulance with large AMI. Immediate transfer and preparation of cath lab and personnel were initiated resulting in a mean door-to-balloon time of 43 minutes (min). If no pre-hospital triage would have been performed, 82 pts (32%) would initially have been admitted to the nearest community hospital without PTCA facilities. If they would subsequently have been referred to a PTCA centre the transporation distance would have increased from an actual 32 ± 9 kilometres (km) to a distance of 51 ± 11 km. Previous studies showed that the mean in-door-out-door time in a community hospital for pts who are candidates for primary PTCA is 45 min.
Conclusion: Pre-hospital identification of pts with large AMI in order to transport them directly to a PTCA centre leads to a considerable reduction in ischemic time as preparation of cath lab and personnel is already initiated. In 32% of pts pre-hospital triage prevents transportation to a centre without PTCA facilities. For this group of pts ischemic time would then increase with at least 60 minutes.

2042 The golden hour of primary angioplasty: reduced in-hospital mortality when door-to-TIMI 3 time is 60 min or less

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While there is a clear relation between time to treatment and survival benefit of thrombolysis for acute myocardial infarction (MI), there is controversy with respect to the same relation when pts are treated by primary angioplasty. Some multicenter studies have suggested that time from admission to angioplasty is better correlated with survival than the time from pain to recanalization. This retrospective single center study evaluated the impact on survival of the time from pain-to-admission and of the time from admission-to-TIMI 3 flow in the infarct-related-artery (IRA), in pts successfully treated with primary angioplasty for ST-segment elevation MI<=6 hours of symptom onset. There were 499 consecutive pts admitted 181±85 min after symptom onset. The mean age was 59±14yrs (26-91), 80% were males. Infarct location was anterior in 47% and 36% had a contraindication to thrombolysis. TIMI 3 flow was achieved in all pts, 54±28 min after admission (75% before 60 min), with stents placed in 36%. Overall in-hospital mortality was 3.2%. Using multivariate analysis, age (OR: 1.79 per 10 yrs, p=0.009), female sex (OR: 3.56, p=0.03) and time from admission-to-TIMI3 (OR: 1.27 per 15 min, p=0.01) were the three independent predictors of mortality. Neither time-to-admission nor time from pain-to-TIMI 3 flow were predictors of mortality. There was a sharp step-up in mortality when admission-to-TIMI 3 flow exceeded 60 min: 1.8% vs 6.7% for pts recanalized within 60 min of admission vs those recanalized later (p=0.01). In this single center study, the time from admission to TIMI 3 cannot be interpreted as a surrogate for center expertise.

Conclusion: there is no clear relation between the time from pain-to-recanalization and survival after primary angioplasty for acute MI. Conversely, there is a "golden hour" of very low mortality when pts can be successfully recanalized within 60 min of admission.

2043 Outcome of acute myocardial infarction patients admitted to hospitals with and without facilities for primary PTCA: data from the AMI-Florence registry

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Background: It is unclear whether the outcome of patients (pts) with acute myocardial infarction (AMI) initially admitted to hospitals without PTCA facilities and then transferred to perform primary PTCA (P-PTCA) is different from that of pts directly admitted to hospitals with P-PTCA programs.

Methods: Data are derived from the AMI – Florence Registry, a prospective observational registry including all the Florence area residents who experienced AMI from March 1, 2000 to February 28, 2001 and were admitted to hospital within 12 hours from symptom onset. Florence area includes 7 hospitals, 5 without the facilities to perform P-PTCA and 2 with specific programs for P-PTCA.

Results: This analysis refers to the 423 pts with ST-elevation AMI included in the registry who underwent P-PTCA. Of these pts, 287 were directly admitted to the 2 centres with PTCA facilities (Group 1) and 141 were initially admitted to the 5 hospitals without PTCA facilities and then transferred to the 2 centres with invasive facilities (Group 2). In term of risk factors and clinical characteristics, a lower prevalence of history of angina was observed in Group 1 (28.7% vs 44.7%, p=0.001); Killip class >1 was observed in 17.7% of Group 1 and 24.8% of Group 2 (p=0.09); cardiogenic shock was present in 6% of Group 1 and 5% of Group 2 (p=0.66). Median time from symptom onset to admission was 135 min in Group 1 and 130 min in Group 2; median door (of the admission hospital)-to-balloon time was 25.5 min in Group 1 and 113 min in Group 2. Door-to-balloon time was < 60 min in 81% of Group 1 and 19% of Group 2 (p<0.0001). TIMI grade 3 flow was restored in 95% of Group 1 and 93.6% of Group 2 (p=ns). Left ventricular ejection fraction of the pts alive at discharge was exactly the same in Group 1 and Group 2 (mean 45±12%). Six-month mortality was 8.2% in Group 1 and 9.9% in Group 2. Comparing mortality in pts with door-to-balloon times < 60 min and >=60 min adjusted for Group 1 or Group 2, no significant difference in mortality was observed.

Conclusion: Despite their higher Killip class and longer door-to-balloon time, pts transferred from hospitals without P-PTCA facilities have an excellent outcome which is comparable to that of pts directly admitted to hospitals with P-PTCA facilities.

2044 Does pre-hospital management of myocardial infarction by medicalized mobile intensive care units improve the outcome of patients undergoing percutaneous coronary intervention

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Background: The influence of prehospital care by Mobile Intensive Care Units (MICU) on the outcome of a mechanical reperfusion strategy has never been assessed. The logistics of pre-hospital management may reduce delays before reperfusion and improve the clinical results of primary angioplasty.

Methods: Between January 1998 and September 2001, 913 patients underwent percutaneous coronary intervention for acute myocardial infarction (AMI) in our institution. Three admission modalities were comparatively assessed: 616 patients (67.5%) were managed by medicalized MICUs before direct admission to catheterization laboratory; 114 patients (12.5%) presented directly to the emergency room and 183 patients (20%) were transferred from tertiary hospitals.

Results: Pre-hospital care patients were comparable with regard to age, male gender, MI location but were more likely to be smokers, to have a history of myocardial infarction and to be receiving thrombolytic therapy (in 20.8% vs. 2.6% for pre-hospital vs. in-hospital care respectively, p<0.0001). Pre-hospital patients had shorter onset to admission delays (254 ± 208 vs. 329 ± 292, p=0.003) and door to stent time (45 ± 53 vs. 77 ± 89 min, p<0.0001) as compared to in-hospital care patients. Patients managed by medicalized MICUs were less likely to have totally occluded arteries before intervention (60.9% vs. 76.2%, p=0.003). Final TIMI 3 grade flow exceeded 90% in all groups without significant differences. Pre-hospital care was associated with a significantly lower in-hospital mortality rate as compared to in-hospital care patients and transfer patients (2.3 vs. 6.1% and 7.1% p=0.004). Multivariate logistic regression analysis revealed that pre-hospital care was an independent predictor of survival (odds ratio, 95 percent confidence interval; p=0.006).

Conclusions: Pre-hospital care delivered by physicians in MICUs improves the outcome of AMI patients treated by percutaneous coronary intervention. The reasons may lie in delay reduction, earlier reperfusion of the infarct-related artery before mechanical reperfusion and improvement of hemodynamic status before admission.

2045 Acute myocardial infarction with normal coronary angiography does not exist. Review of 625 coronary angiograms from the PRAGUE-1 and -2 studies

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Aim: Despite the extensive existing literature on acute myocardial infarction (AMI) with normal coronary arteries (NCA) our experience with primary percutaneous coronary intervention (p-PCI) is different. Thus, we hypothetized, that NCA in the acute phase of evolving AMI does not exist.
Methods: "PRAGUE-1" and "PRAGUE-2" studies randomized patients with ST elevation AMI to immediate on-site thrombolysis or transport for p-PCI. 625 coronary angiograms performed within 2 hours of initial ECG were retrospectively analyzed for presence of NCA (defined as absence of visible angiographic signs of atherosclerosis, thrombosis or spontaneous spasm). Symptoms of ischemia were persisting during angiography in 563 pts., while in 62 pts. symptoms disappeared during the transportation to angiography.
Results: NCA were found in 13 patients (2% of all acute phase angiograms). The clinical characteristics of these patients:
* Pain was lasting at the time of acute phase angiography in 1 pt. (in 12 pts. pain disappeared during the transport - before the start of coronary angiography).
* ECG site of "AMI" was inferior in 7 pts., anterolateral in 5 and LBBB in one.
* Amplitude of ST elevations was 0-2 mm in 11 pts., >2 mm in 2.
* CK-MB was negative in 7 and positive in 6 pts., mean was 1,72 ukat/l
* LV function was normal in 6 pts., diffuse hypokinesis in 4 and regional akinesis in 3. Mean ejection fraction (EF) was 51%.
* The discharge diagnosis was small myocardial infarction in 4 pts. (= 0,6% of all pts.), acute myocarditis in 2 pts., dilatation cardiomyopathy in 2 pts., hypertension in 2 pts., pulmonary embolism in 1 pt. and misinterpretation of ECG (no cardiac disease) in 2 pts. All 4 patients with small AMI underwent angiography 30 – 90 minutes after the complete relief of the signs of acute ischemia. All had normal EF. Transient coronary spasm disappearing before angiography was assumed to be the cause for these small infarcts. Among 563 pts. catheterized during ongoing symptoms of ischemia none had normal coronary angiogram.
Conclusion: The incidence of normal coronary angiography in the acute phase of suspected AMI is 2%. Most of these cases represent wrong diagnosis. The incidence of normal coronary angiography in biochemically confirmed AMI is 0,6%. Normal coronary angiography (when performed during the ongoing symptoms of ischemia) in acute myocardial infarction does not exist.

2046 The time point of platelet blockade is critical in patients with acute myocardial infarction undergoing percutanous coronary intervention

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Background: Blood thrombogenicity is high in patients with acute myocardial infarction (AMI). Newer trials point to the clinical benefit of early antiplatelet therapy when treating those patients with percutanous coronary intervention (PCI). Our study aimed to investigate whether the time point of abciximab administration (before versus during PCI) influences in vivo platelet-leukocyte interaction in patients with AMI.
Methods: 34 patients with AMI were treated with PCI. The time point of abciximab treatment was chosen 1.) one hour before coronary intervention and 2.) after the reopening of the infarct related artery had been acchieved, resulting in 8 times abciximab administration before and 26 times during PCI. Blood samples were obtained without torniquet before and immediately after intervention and the number of platelet-leukocyte aggregates in blood indicating the blood thrombogenicity was analysed by flow cytometry.
Results: In vivo platelet-leukocyte aggregation was comparable in patients treated one hours before and during intervention with abciximab (3,7% ± 1,0 versus 3,8% ± 1,2; n.s.). After performing the coronary intervention with successful reopening of the infarct related artery, there was a significant decrease in platelet-leukocyte aggregates in patients who received abciximab at an early time point one hour before the intervention had started (3,7% ± 1,0 before versus 3,4% ± 1,1 after intervention). In patients who received abciximab for the first time during coronary intervention and after vessel reopening, platelet-leukocyte aggregates were increased at the end of the intervention (3,8% ± 1,2 before versus 4,3% ± 1,4 after intervention); $p<0,05$.
Discussion: In order to reduce blood thrombogenicity in patients with an acute myocardial infarction, the time point of GPIIb/IIIa blocker administration has to be as early as possible before performing PCI. Our results confirm the clinical benefit reported in trials on AMI, in which abciximab was given as early as in the ambulance on the way to the hospital.

PERCUTANEOUS CORONARY INTERVENTION: VARIATIONS IN STENTING, CUTTING AND SPOTTING

2047 Direct stent implantation does not lead to a reduction in restenosis; a randomized controlled trial

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Objectives: This study compared the 6-month angiographic and clinical results of direct stenting versus stenting after balloon predilatation.
Methods: Four-hundred patients with angina pectoris and/or myocardial ischemia due to non-occlusive coronary stenoses in a single native vessel were randomized to either direct stenting versus stenting after predilatation. Demographic characteristics were evenly distributed in both groups. The angiographic results, and clinical outcomes associated with the two procedural strategies up to six month were compared.
Endpoint definitions: (1) Procedural success, (2) binary restenosis and (3) major adverse cardiac and cerebral events (MACCE) were defined as (1) a successful procedure without in-hospital events, (2) luminal narrowing >50% at six month and (3) composite incidence of death, myocardial infarction, ischemia-driven revascularization and cerebral events, respectively.
Results: Successful stent implantation was achieved in 98.3% for direct stenting and 97.8% for stenting preceded by predilatation, whereas the primary success rate of direct stenting was 88.3% (p=0.01). Procedural success rates were similar (96.0% vs. 94.5%). The angiographic follow-up at six month included 333 of the 400 patients (83%). The binary in-stent restenosis rates among the 163 direct stented and 166 predilated patients who underwent follow-up angiography were 23.1% and 18.8% respectively (p=0.32). At the end of a mean observation period of 185±25 days overall late MACCE had occurred between start procedure and the end of follow-up in 31 of 200 (15.5%) patients randomized to direct stenting, versus 33 of 200 (16.5%) randomized to predilatation (ns).
Conclusions: Direct stenting did not lead to a reduction in restenosis and was associated with similar procedural success rates and clinical outcomes as compared to the strategy of stenting preceded by balloon predilatation.

2048 Analysis of long-term results after primary stenting in comparison with balloon predilatation before stenting

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Background: Primary stenting (PS) without predilatation (PD) may lead to reduced coronary vessel trauma. This could result in a lower rate of restenosis (RR).
The aim of our study was analysis of the influence of this strategy on long-term follow up (FU).
Material and methods: Last four years we prospectively registered all interventions in a database. The first treated lesion of each patient with FU angiography after 6 months or earlier with restenosis was eligible for evaluation. 1347 interventions with PTCA followed by stent implantation (ST) as well as 1104 with PS were analyzed by quantitative coronary angiography. First the balance of well-known predictors for restenosis like reference diameter (RD), lesion type, diameter stenosis before treatment and other factors was analyzed. Accounting for the bias created by the imbalance of some of these factors between the two treatment arms, the influence of the technique on long-term result was investigated by multifactorial ANOVA with regard to % diameter stenosis at FU. A multiple logistic and general stepwise regression analysis was performed with regard to binary restenosis rate (>50% stenosis at FU) and the amount of stents/lesion.
Results: PD was more often performed in type B2 or C lesions (77% vs. 45% in type A and B1, $p<0,001$), in small vessels (median RD 2.57 mm vs. 3.24 mm with PS, $p<0.001$) and in more severe stenoses (median diameter stenosis 96% vs. 79% in PS, $p<0.001$). Long-term results showed a smaller mean diameter stenosis at FU after PS (32% vs. 45%), which remained significant in MANOVA (p=0.02). Multiple logistic regression revealed as independent predictors for binary restenosis: type B2 or C lesions (OR 2.3, p=0.005), PS (OR 1.9, p=0.01), reference diameter (OR 1.7, p=0.02), Diabetes mellitus (OR 1.5, p=0.04) and multiple stenting (OR 1.8, p=0.01). Independent predictors by general stepwise regression for diameter stenosis before treatment (OR 1.0, p=0.05), multiple stenting were PS (OR 1.2, p=0.03) and type B2 or C lesions (OR 2.2, p=0.005).
Conclusion: Diameter stenosis at FU and restenosis rate are significantly lower with PS as compared with PD followed by ST. The amount of stents/lesion is significantly lower after PS vs. PD followed by ST too. Thus whenever PS without PD is feasible it must performed for improvement of long-term results of coronary interventions.

2049 Feasibility and safety of transradial coronary angiography followed by ad hoc percutaneous coronary intervention

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Transradial artery cannulation is a useful alternative approach to the performance of diagnostic and interventional coronary procedures. The purpose of the study is to evaluate the safety of the radial (R) approach compared with the femoral (F) access in coronary angiography followed by had hoc PCI. A total of 591 patients (pts) met the clinical criteria of our comparative study (no cardiogenic shock or humeral approach). The pts were divided into 2 groups [R (328, 55%), F (263, 45%)]. We compared radiation dose and 1 year-outcome of major cardiac events (cardiac deaths, MI, CABG, repeat PCI) between groups. There were slight differences in baseline data between the both procedures [(R:F) mean age; 66 yo:65 yo, male gender; 77%:75%, prior MI; 27%:36%, $p< 0.05$, multivessel disease; 50%:60%, $p< 0.05$. Ten percent of R procedures were converted into femoral or humeral access. Failure to achieve PCI, to stent and to direct stent the lesion were identical (5% vs 5%, 0.6% vs 1.9%, 3% vs 4%, respectively). Radiation time were higher in the R group than in the F group (23±12 min vs 17±4 min, $p< 0.001$) as well as the dose area product value (27753±15750 R*cm^2 vs 21264±13427 R*cm^2, $p<0.001$). Non cardiac complications occurred in 5 (1.5%)R pts (2 vascular surgical repairs, 2 cerebrovascular events and one cardiac tamponade leading to death) and in 4(1.5%)F pts(4 vascular surgical repairs leading to one death). The cardiac event-free ratio were 13% in both groups [(R:F) death; 0.6%:1.1%, MI; 2%:2%, CABG; 0.9%:1%, repeat PCI; 9%:8%].

The radiation dose to patients, staff members and physicians is higher when the transradial cannulation is prefered to the femoral access for coronary angiography followed by had hoc PCI. Both methods give same immediate and long term results.

2050 Treatment of "false bifurcation lesions" with coronary stenting

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Background: Due to the axial plaque redistribution phenomenon in the side branch, "false bifurcation lesions" become frequently "true bifurcation lesions" after coronary stenting. Consequently, we have developed a systematic and simple strategy for stenting these lesions: wiring of both branches, then stenting of the main branch with a jailed wire, kissing balloon inflation and provisional T stenting of the side branch.

Methods: The purpose of this study was to retrospectively evaluate the immediate results and mid term outcome of this specific approach in type 2 lesions (Lesion proximal and distal to the bifurcation without significant lesion of the side branch), type 3 (lesion of the main branch proximal to the bifurcation) and type 4a (lesion distal to the bifurcation). All patients (cardiogenic shock excluded) had been prospectively included in a prospective single center observational database since January 1996 with 7-month follow-up and coronary angiogram in cases of clinical or stress test ischemia.

Results: Among 936 bifurcation lesions consecutively included, 452 (49%) were "false" and 319 treated by this approach. The clinical characteristics were similar in each group. Main characteristics and results are summarized in the table below:

	Type 2	Type 3	Type 4a
Patients (n)	120	95	79
Age (years)	64±12	62±13	63±13
LAD-diagonal (%)	55.4	32.5	52.2
Proximal reference (mm)	3.09±0.51	3.28±0.63*	3.14±0.59
Stenosis (%)	73.1±14.6*	69.6±15.3	66.6±12.5
Side branch stent (%)	18.5	19.5	14.9
Kissing balloon (%)	89.0	85.1	97.0
Angiographic success 2 branches (%)	96	95	100
In-hospital MACE (%)	4.4	1.3	1.5
Total 7-month MACE (%)	11.5	5.4	18.5*
TVR 7-month (%)	7.5	5.4	16.7*

* $p<0.05$

Conclusion: this study shows that provisional T stenting of the side branch for treating "false bifurcation lesions" is associated with a high success rate and acceptable MACE and TVR rates

2051 Low restenosis rate after spot stenting used as a standard procedure

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The restenosis rates of short stents is lower than that of longer stents. However, stents with a length of > 10 mm are used for most procedures. We investigated the feasibility of routinely used spot stenting. The protocol suggested predilatation in order to achieve a sufficient result. In the case of a residual stenosis > 30% (immediately after PTCA or after waiting 5 min) and a length of the residual stenosis < 8 mm a short stent (< 10 mm) was implanted using an inflation pressure > 14 atm. A stent diameter was chosen as to achieve a 1.1 ratio to the diameter of the reference segment at the inflation pressure used. Spot stenting without predilatation was allowed at proximal sites of the LAD and RCA. This protocol was followed in 305 consecutive patients (pts.) receiving 337 coronary interventions (Int.). In 95 Int. no stent was used because of an optimal PTCA result (n=45), a small coronary diameter (n=26), treatment of a stent restenosis (n=19) or because of the presence of diabetes (n=5). A longer stent (>10 mm) was used in 41 Int. because of the necessity to cover a dissection (n=34) or a longer residual stenosis (n=7). Spot stenting was performed in 201 Int. (Multilink 8 mm 135x; NIR 9 mm 76x) with a nominal diameter of 3.2± 0.4 mm, implanted at an inflation pressure of 13.7 ± 3 atm. Procedural success was achieved in 97.7% of pts. During the 6 month follow-up one pt. died, all others were event free. Control angiography was done in 284/301 (94%) pts. eligible; target lesion revascularization rate (TLR) at 6 months was calculated for all patients.

Long-term Results

	No Stent	Long Stent	Spot Stent	All lesions
Restenosis	7/77 (9%)	7/39 (18%)	26/182 (14%)	40/298 (13.4%)
TLR	7/77 (9%)	5/41 (12%)	20/186 (11%)	32/301 (10.6%)

Conclusions: Spot stenting in feasible in most interventions yielding a low restenosis rate. The use of the proposed procedure reduces restenosis rates in all interventionally treated patients.

2052 Cutting balloon angioplasty is superior to balloon angioplasty and stent for the treatment of small coronary artery. "Dual center experience"

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Background: The best interventional strategy to treat lesions in the small coronary artery has not been yet established. It has been proposed that cutting balloon angioplasty (CBA) may be effective strategy for the treatment of small coronary artery disease.

Methods: We analyzed a total of 255 small coronary artery disease from two institutions treated either by stent (65 lesions), CBA (65 lesions), and Balloon angioplasty (BA: 125 lesions). Small coronary artery was defined as a vessel with a reference vessel diameter of < 2.7mm. Six months angiographic follow-up was performed in all cases. Clinical events, angiographic restenosis, and QCA results was compared among 3 groups.

Results: There was no difference in baseline characteristics. Analyzed data are shown in table.

	BA	CBA	STENT	p value
No. of lesion	125	65	65	ANOVA
Diabetes Mellitus, %	37.5	42.2	32.8	ns
Ref diameter, mm	2.13±0.32	2.22±0.34	2.10±0.31	ns
Pre MLD, mm	0.63±0.34	0.72±0.33	0.57±0.37	ns
Pre % stenosis	71±15	68±14	73±17	ns
Lesion length, mm	14.3±7.7	12.7±9.0	14.8±6.0	ns
Post MLD, mm	1.76±0.30	2.10±0.40	2.30±0.30	<0.0001
Post % stenosis	25± 9	18±11	10± 7	<0.0001
Acute gain, mm	1.1±0.4	1.4±0.4	1.7±0.4	<0.0001
Late loss, mm	0.5±0.5	0.6±0.5	1.0±0.6	<0.0001
Loss index	0.47±0.47	0.47±0.42	0.62±0.34	ns
Restenosis rate, %	48.7	31.1	41.3	0.078
In hospital event, %	6.3	1.6	3.1	0.26

In hospital event = cardiac events included subacute stent thrombosis

Conclusions: The CBA for small coronary artery disease provided superior outcome in angiographic restenosis and safe compared to the other strategy. These findings suggested that CBA is a useful strategy for the treatment of small coronary artery disease.

PERCUTANEOUS CORONARY INTERVENTIONS: WHOM TO TREAT OR NOT TO TREAT

2053 Fractional flow reserve after stenting to predict repeated target vessel revascularization during follow-up

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Background: In-stent restenosis occurs in approximately 15% of patients despite optimum angiographic results. Coronary pressure measurement has been suggested as an additional physiologic method to optimize stent deployment. Aim of the present study was to investigate the predictive value of pressure-derived fractional flow reserve (FFR), measured immediately after stenting, for repeated target vessel revascularization (TVR) at 6-month follow-up.
Methods: In 750 patients in 15 hospitals, stent implantation was guided by coronary pressure measurement and post-stent FFR was calculated as the ratio of hyperemic coronary pressure just distal and just proximal to the stented segment. Patients were divided in 5 groups, according to the post-stent FFR: 0.96-1.0; 0.91-0.95; 0.85-0.90; 0.81-0.85; and 0.75-0.80.
Results: Baseline characteristics, procedural characteristics and angiographic results were completely comparable in all groups. A strong inverse correlation was found between post-stent FFR and need for TVR and event rate at 6-month, ranging from 4% in patients with complete normalization of FFR after stenting to 41% in the worst group (table). Patients with FFR <0.90 had a relative risk for restenosis that was almost 5x higher than in patients with FFR >0.90.

Post-stent FFR	0.75-0.80	0.81-0.85	0.86-0.90	0.90-0.95	0.96-1.0	all patients
number of pat	44	63	130	241	266	750
refer diam (mm)	2.8 ± 0.5	3.0 ± 0.6	2.9 ± 0.5	3.0 ± 0.6	3.2 ± 0.5	3.1 ± 0.6
post-stent stenosis	12 ± 9%	8 ± 13%	10 ± 10	7 ± 8%	7 ± 10%	9 ± 11%
TVR rate	41%	25%	20%	7%	4%	13%

Conclusion: FFR after stent implantation is a strong independent parameter to predict need for target vessel revascularization (TVR) at 6-month follow-up. Complete normalization of FFR after stent implantation can be achieved in 40% of the patients and is associated with a 6-month restenosis rate of 4% only.

2054 Coronary intervention in the elderly: comparison on immediate and long-term clinical outcome between octogenarians versus septuagenarians

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Background: Cardiologists will face more often the difficult clinical dilemma of the decision making for elderly patients with symptomatic coronary artery disease. The aim of this study is to evaluate the immediate and long-term clinical results following elective percutaneous coronary interventions in elderly patients comparing septuagenarians versus octogenarians.
Methods: Between January 1997 and August 2001, 521 consecutive patients,150 octogenarians (mean age of 83±2.86 yrs) and 371 septuagenarians (mean age of 73.3±2.7 yrs) underwent elective percutaneous coronary intervention (PCI) at our institutions. The data reported are related to all the patients in whom coronary intervention was performed or intended. Major Adverse Cardiac Event (MACE) was defined as death, Myocardial Infarction (MI) and repeated revascularization either by Re-PCI or Coronary Artery By-Pass Grafting (CABG). MACE occurrence in hospital and at 6-month follow-up was the study end-point.
Results: Octogenarians were more often females (34.6% vs 22.1%;p=0.039), with a lower rate of previous PTCA (10.6% vs 23.1%; p=0.0009) and more calcified lesions (26.6% vs 18.3%; p=0.04). No difference was found in terms of multi-vessel intervention between the two groups (37% in octogenarians vs 34% in septuagenarians; p=0.5). Angiographic success was higher in septuagenarians (99.4% vs 97.3%; p=0.0001) as the rate of complete revascularization (52.5% in septuagenarians vs 40% in octogenarians;p=0.04). No significant differences in hospital mortality (2% in octagenarians vs 0.5% in septuagenarians; p=0.1), MI (2% in octogenarians vs 1.6% in septuagenarians; p=0.7) and emergency repeated revascularization (0.2% vs 0.0%; p=0.1) were observed. At 6-month follow up, mortality (7.3% vs 2.7%; p=0.02) as well as MI (4.0% vs 1.8%: p=0.2) were higher in octogenarians but were counterbalanced by a lower rate of repeated revascularization (4.1% vs 11.3%; p=0.01) with no difference in terms of event-free survivals between the two groups (84.3 vs 84.6;p=0.9). Multivariate logistic regression (figure 1) showed that age(RR:1.1; 95%CI 1.01-1.20) and complete revascularization (RR:0.11;95%CI:0.02-0.53) are independent predictors of 6-month mortality.
Conclusion: PCI in octogenarians has a similar acute mortality but a higher late mortality than in septuagenarians. This higher mortality is possibly explained by the lower rate of complete revascularization achieved.

2055 Short-term outcome after percutaneous coronary interventions in patients affected by solid cancer and acute coronary syndromes

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Background: The number of pts affected by tumours (K) and acute coronary syndromes (ACS) is increasing constantly in the industrialized countries. It is well known that pts affected by malignancies who need myocardial revascularization may benefit more from percutaneous intervention (PCI) than surgery (due to the severe decrease in immuno-system defenses during CABG). In addition, since malignancies induce an hypercoagulable/aggregation state, we hypothesized that pts affected by K and undergoing PCI may have a different clinical outcome compared to standard population cohort due to thrombotic complications. Methods and Results: Patients affected by K (n=233) and submitted to PCI at the Mayo Clinic from 1985 to 2000 were retrospectively compared with a standard general population cohort (n=699). Patients were matched as regard of age, sex, ejection fraction, clinical onset of ACS, and cardiovascular risk factors. Significant difference in MACE was present at thirty-day follow-up in the two study group (Table).

Table: 30-Days MACE after PCI

	Tumours (n=233)	Standard Population (n=669)	P value
Mortality (n, %)	11 (4.9)	17 (2.5)	.003
Death/MI	43 (18.5)	46 (6.9)	.0001
Death/ MI/TVR	50 (21)	63 (9.4)	.0001
Emergency CABG	3 (1.3)	8 (1.4)	NS
Coronary Embolization	18 (7.7)	11 (1.6)	.00001
Coronary Occlusion	2 (0.7)	5 (0.7)	NS
Branch Occlusion	12 (5.2)	23 (3.4)	NS
Cardiogenic Shock	11 (4.7)	29 (4.3)	NS

Conclusions: Pts affected by malignancies submitted to coronary intervention for ACS have a worst short-term clinical outcome compared to standard population. This may be due to a severe thrombophilic state leading to increased rate of thrombotic complications after PCI. Prospective clinical studies are necessary to understand if pharmacological intervention that inhibit the coaugulation/aggregation state may improve the clinical outcome of pts affected by both K and ACS submitted to PCI.

2056 Percutaneous coronary intervention of complex lesions is still associated with increased in-hospital and 1-year adverse event rates

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Advances in percutaneous coronary intervention (PCI) have reduced complications but expanded the indications. This study evaluated whether the PCI of complex lesions is associated with increased adverse clinical events for up to 1 year after the procedure. A total of 4629 patients (pts) undergoing PCI between 7/97-2/98 and 2/99-6/99 were enrolled in the NHLBI Dynamic Registry. A complex lesion was defined as a significant stenosis with thrombus, calcification, ostial or bifurcation location or a chronic occlusion. The 2839 pts treated for complex lesions (61.3%) were significantly older and more likely to present with an acute coronary syndrome. PCI of a complex lesion was more likely to cause major dissection, distal embolization, side branch occlusion or persistent reduced blood flow (all $p<0.05$) and the procedural success rate was lower (89.9% vs 96.7%, $p<0.001$). Pts with complex lesions had increased in-hospital and 1-yr event rates ($p<0.001$, table).

Lesion complexity and clinical events

Complex?	In-hospital			One-Year		
	Death	Death/MI	MACE	Death	Death/MI	MACE
Yes	2.0%	5.2%	6.6%	6.2%	11.7%	27.2%
No	0.6%	2.4%	2.9%	3.7%	7.5%	23.3%

All differences $p<0.001$

Additionally, there was a significant trend ($p<0.001$) in increased in-hospital and 1-year death and death/MI rates with increasing number of treated complex lesions. Multi-variate analysis demonstrated that pts with thrombus had a greater incidence of in-hospital death/MI (OR=1.97; 95% CI= 1.35-2.87) while thrombus, calcification,and bifurcation were associated with a greater incidence of adverse events (Thrombus [OR=1.82 95% CI=1.30-2.56], calcification [OR 1.39, 95% CI=1.04-1.85], bifurcation [OR=1.46 95% CI=1.02-2.09]. At 1-yr calcified and bifurcation lesions were independently associated with increased death/MI/CABG (RR=1.18; 95% CI=1.00-1.40, RR=1.34, 95% CI 1.09-1.64, respectively).

In conclusion, PCI of complex lesions was associated with increased periprocedural, in-hospital and 1-yr adverse events. An increased in-hospital event rate was noted independently for thrombotic, bifurcation and calcified lesions. bifurcation and calcified lesions were independently associated with worse long-term event rates.

2057 Non-intervention strategy for patients with significant in-stent restenosis on angiography: 3-year clinical follow-up

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In-stent restenosis remains a major limitation after coronary stent implantation with high recurrent restenosis rate after any interventional procedure.

The aim of our study was to evaluate the long-term clinical outcome of patients (pts) presenting with significant in-stent restenosis on repeat angiography and who were maintained on medical treatment alone with no revascularisation procedure. Clinical follow-up was obtained by phone.

Results: Between january 1996 and may 2000, we could retrospectively identify 258 pts presenting with significant angiographic (> 50% by QCA) in-stent restenosis: among them, 66 (26%) did not undergo percutaneous coronary intervention and/or bypass surgery and were maintained on medical treatment alone. This subset of Pts represented our study group. In this population, repeat angiography was either performed on systematic basis (44 Pts) or because of documented ischemia and or angina < class 2 of the Canadian Classification (22 Pts). Mean age was 61 ± 11 years and 86% were male. In-stent restenosis was diffuse in 84% and mean stenosis diameter was 57 ± 7%. Clinical indications for stent implantation were: unstable angina (28%), acute myocardial infarction (16%), stable angina (56%). Mean stent diameter was 3.0 ± 0.3 mm and mean stent length was 16.5 ± 5.5 mm. Vessel location was LAD in 51%, LCX in 19% and RCA in 26%. Ejection fraction was 62 ± 12% and 60% of pts were pluritroncular. Clinical follow-up was obtained at 33 ± 10 months in all pts: 2 pts died and none developed myocardial infarction. During follow-up, 6 pts (9%) only had target lesion revascularisation (repeat PTCA). Event-free survival was 86% at 33 months.

Conclusions: Medical treatment alone is associated with a good long-term clinical follow-up in selected patients with significant documented in-stent restenosis. Knowing the high recurrent restenosis rate after repeat interventional procedures for in-stent restenosis, medical treatment alone is a valuable alternative in non or pauci-symptomatic pts, even in case of diffuse restenosis.

2058 Asymptomatic restenosis after coronary artery stenting – Is re-PTCA indispensable?

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Background: Coronary artery stenting has reduced bailout situations and the restenosis rate after percutaneous coronary interventions (PCI) but restenosis still limitates the long-term outcome. The diagnosis of a hemodynamic relevant restenosis is not standardized and the treatment options of restenosis are discussed controversially.

Methods: In an unselected population of 397 patients we analyzed the therapeutic strategy in case of an angiographically assessed restenosis (diameter stenosis > 50%) three months after coronary artery stenting. Recurrent angina or myocardial ischemia had been required for the primary intervention.

Results: A total of 105 patients (61.1+10.1 years, 72.4% male) presented a significant restenosis in the target lesion measured by quantitative coronary angiography. Among the population with restenosis 65 patients (61.9%) presented recurrent angina, 50 patients (47.6%) showed myocardial ischemia during stress tests. Twenty-two patients (21%) had no angina and no ischemia. PCI of the target lesion was performed in 70 patients (66.7%), in 12 patients (11.4%) a surgical revascularization was recommended because of multivessel disease. A total of 24 patients (22.9%) with restenosis were treated without intervention. In this conservatively treated group 6/24 patients presented uncertain symptoms and unclear ischemia. In 2/6 patients a PCI had to be performed due to new angina in the following weeks.

Conclusion: Treatment strategies of restenosis after corononary artery stenting are not standardized. The indication for re-intervention should include clinical, functional, morphologic and prognostic factors. In case of absence of angina or myocardial ischemia an observant regimen seems to be reasonable.

PRIMARY STENTING IN ACUTE MYOCARDIAL INFARCTION. PERCUTANEOUS CORONARY INTERVENTION VERSUS THROMBOLYSIS

2059 A cautionary tale for multivessel stenting during acute myocardial infarction: significant vasoconstriction of non-culprit lesions

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Recently there has been a worldwide trend towards multivessel stenting in the setting of myocardial infarction, treating nonculprit lesions as well as the infarct-related lesion. However, not infrequently we noted that nonculprit lesion severity was significantly exaggerated by vasoconstriction at the time of infarction, raising the possibility that many non-culprit lesions may not need to be treated. In this retrospective study we identified all patients in our infarct interventional database who had a lesion of >50% stenosis (by operator report) in a non-infarct related artery and had additional angiography within 9 months of the index infarction. Angiographic stenosis was measured in each study by the QCA Medis system in orthogonal planes by operators blinded to study sequence. Patients (n=46) were excluded if matching angiographic views were not obtained or when coronary artery bypass grafting had been performed to the study vessel. Mean (SD) minimal lumen diameter of non-culprit stenosis(n=59) increased significantly from infarct angiography (I) to non-infarct angiography (NI) (I 1.53 (0.51) vs NI 1.78 (0.65) $P < 0.0001$) while % stenosis reduced (I 49.3 (14.5) vs NI 40.4 (16.6) $P < 0.001$). Reference diameter was not significantly different (I 3.1 (0.8) vs NI 3.0 (0.8)). Medications, hemodynamics, clinical status and demographics were compared between studies but did not influence non-culprit stenosis severity on multivariate analysis. 10/59 lesions were > 50% stenosis during the infarct study and < 50% at the non-infarct study [MLD 1.14 (0.37) mm vs. 1.76 (0.70) mm, $p<0.0001$, and % stenosis 61.1 (9.1) % vs. 38.0 (6.3) %, $p<0.0001$]. We conclude that clinically significant vasoconstriction is common in non-culprit lesions at the time of infarction and aggressive intracoronary vasodilator administration may be advisable prior to treating non-culprit lesions at the time of infarction.

2060 Randomised comparison of direct stenting and stenting after predilatation in acute myocardial infarction. In-hospital results of DIRAMI trial

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Background: Data on utilisation of direct stenting technique during immediate angioplasty in acute myocardial infarction (AMI) patients (pts) are limited. The aim of this on-going study is to evaluate feasibility, safety and effectiveness of direct stenting in AMI.
Methods: Consecutive pts with AMI were randomised before angiography to direct stenting (DS) or stenting after balloon predilatation (PS). Exclusion criteria were pulmonary oedema and cardiogenic shock. After coronary angiography pts were excluded if the operator decided not to perform angioplasty or stenting. TIMI flow grade 0 or 1 were not considered a contraindication for DS. One-year clinical and angiographic follow-up is pending. Analysis was performed on an intention to treat basis.
Results: Between Nov. 2000 and Sep. 2001, a total of 248 pts were randomised: 125 to DS and 123 to PS. After coronary angiography 31 pts were further excluded. Final study groups comprised 110 and 107 pts in the DS and PS groups, respectively. Cross-over to predilatation occurred in 13 (11.8%) in DS group (inability to cross the lesion with a stent - 7, uncertain guidewire placement - 4, lesion type - 2 pts). Except 2 pts (1 per group) the stents were successfully implanted. Procedural and clinical in-hospital outcome is summarised in the table.

In-hospital outcome

	DS (N=110)	PS (N=107)	P
TIMI flow grade 3, %	95.4	93.5	0.52
TMP* grade 2 or 3, %	81.3	76.2	0.41
MLD, mm (SD)	2.66 (0.41)	2.70 (0.52)	0.46
Additional stent(s), %	12.7	14.9	0.63
Side branch occlusion, %	2.7	3.7	0.72
Fluoroscopy time, min (SD)	12.2 (7.5)	14.9 (7.7)	0.011
Procedure time, min (SD)	59 (22)	72 (31)	0.0006
Reocclusion or reinfarction, %	1.8	2.8	0.68
Death, %	0	1.9	0.24

* TMP (TIMI Myocardial Perfusion) grade was accessible in 83% in DS group and 78% of pts in PS group.

Conclusions: Direct stenting during angioplasty for AMI is feasible, safe and effective in a majority of patients suitable for stent implantation. Follow-up data are required to define the usefulness of direct stenting technique in patients with AMI.

2061 Does plaque characteristics influence the late outcome after primary stenting for acute myocardial infarction?

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Background: Previous studies have reported that acute myocardial infarction (AMI) is mainly associated with a soft plaque accompanying positive arterial remodeling. The aim of the study was to assess the relationship between ultrasonic features of the lesion and late outcome in patients with AMI undergoing primary angioplasty.
Methods: The study population consisted of 53 patients (12 F; 41M; mean age 55 y) with totally occluded infarction related artery. Intracoronary ultrasound was performed after predilation (4-6 atm) with a small balloon (1,5-2,0 mm) using 20 MHz electronic probe (Avanar, Jomed Inc). Ultrasonic images were recorded during automatic pullback manouever (speed 1,0 mm/sec) for their qualitative and quantitative assessment. Media to media diameter and total vessel area were calculated in the proximal and distal reference segments and also at the site of artery occlusion. Additionally, a remodeling index was calculated (total vessel areas at: occlusion site /average of prox and dist reference segments). Its value below 0,95 was the cut off for negative remodeling. Studied population was divided into 2 groups: Gr 1 with negative remodeling (35 patients) and Gr 2 with positive remodeling (18 patients) in examined arteries. During 6 months follow-up we recorded evidence of MACE (death, myocardial infarction, target vessel revascularisation).
Results: Stent was implanted successfully in every patient. The mean nominal stent diameter was 3,34±0,26 mm in Gr 1, and 3,86±0,51mm in Gr 2 ($p<0,05$). Mean stent area after intervention was 7,54±2,31 vs 8,56±2,98 mm^2, respectively Gr1 vs Gr2, p=NS. Calcific plaque (arc of calcium >180) was found in 74% and 33% of cases in Gr 1 and Gr 2, respectively ($p<0,05$). Remodeling index was significantly smaller in Gr 1 in comparison with Gr 2 (0,64±0,21 vs 1,12±0,11; $p<0,05$). Furthermore mean plaque burden at the occlusion site was significantly smaller in Gr1 than in Gr2 (59,2±12,3 vs 68,7±14,1 respectively, $p<0,05$). During follow up, the evidence of MACE was significantly higher in Gr1 than in Gr2 (28% vs 12% respectively, $p<0,05$). The strong correlations between remodeling index and MACE (r=0,79, $p<0,05$) and arc of calcium and MACE (r=0,61, $p<0,05$) were also found.
Conclusion: Negative remodeling with accompaning significant calcification is very frequent in AMI related artery. This plaque presentation is related with worse late outcome after primary stenting.

2062 Primary PTCA compared to early thrombolysis in patients with acute myocardial infarction: Results of the Berlin Myocardial Infarction Registry

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Introduction: There is evidence that primary percutaneous coronary intervention (PCI) after acute myocardial infarction (AMI) is an alternative to early thrombolysis if performed in a timely fashion by experienced interventionel cardiologists in high volume centers. Since Berlin has many high volume centers with experienced personnel, the study compared in-hospital mortality of patients with AMI treated with primary systemic thrombolysis and primary PCI.
Methods and results: Using data from the Berlin Myocardial Infarction Registry on 2945 patients with acute myocardial infarction in 1999/2000, in-hospital mortality of patients treated with primary PCI compared to those treated with thrombolysis was examined. 59% of all patients received reperfusion therapy. Patients who received reperfusion therapy had a much lower unadjusted in-hospital mortality rate than patients who did not receive reperfusion therapy (8.6% versus 19.3%, $p<0.05$). Of those patients who did receive reperfusion therapy, 57% received intravenous thrombolytic therapy, 43% received primary PCI. Patient characteristics were similar in both groups (age, sex, diabetes mellitus, congestive heart failure etc.). Statistically significant differences between both groups were observed only for: diagnostic first ECG, time since onset of symptoms to hospital <3hours, on site facility for invasive cardiovascular procedures in the admitting hospital ($p<0.05$).
After adjusting for significant differences in baseline and clinical characteristics (age, sex, diabetes mellitus, hypercholesterinaemia, congestive heart failure/previous MI at admission, cardiogenic shock/heart failure at admission, pulmonary oedema, anterior MI), the difference in in-hospital mortality between the patients treated with PCI and those treated with thrombolysis was not significant anymore (OR=0.67, 95%CI:0.41-1.1). A different methodological approach (case control study with individual matching) revealed the same results.
Summary: The data of the Berlin Myocardial Infarction Registry from 1999 and 2000 show that after adjustment for confounding parameters the difference in in-hospital mortality between the patients treated with primary PCI and those treated with thrombolysis was not statistically significant.

2063 Reperfusion therapy with thrombolysis or primary PTCA for acute myocardial infarction in the real world: data from the nation-wide French USIC 2000 registry

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Though randomised studies have shown that primary PTCA was superior to intravenous thrombolysis in patients with acute myocardial infarction, its applicability in everyday clinical practice may limit the extent of this beneficial effect. The nation-wide French USIC 2000 study is a registry which included all patients admitted to ICUs for AMI < 48 hours from symptom onset in November 2000. More than 80% of the ICUs in France participated in the study. Of the 2320 patients recruited, 974 had Q wave or ST segment elevation MI with reperfusion therapy with either primary PTCA within 24 hours of admission (group P, n=429) or thrombolysis (group T, n=545).
Baseline characteristics were quite similar for the 2 groups (age: 61 ± 14 vs 61 ±14; women: 23% vs 22%; hypertension: 38% vs 37%, current smoking; 24% vs 23%, history of CHF: 2% vs 2%). In Group P, however, diabetes mellitus (20% vs 14%, p=0.01), history of MI (17% vs 10%, p=0.0001), and history of PTCA (13% vs 6%, p=0.001) were more prevalent than in group T. More Group P patients had anterior myocardial infarction (46% vs 37%, p=0.002). A similar proportion of the patients (11% vs 12%) were referred from other institutions. In thrombolysed patients, 280 (51%) underwent subsequent PTCA within 24 hours. The in-hospital clinical course was similar in the 2 groups. Five-day mortality was 4.9% in group P vs 5.5% in group T (8.7% in patients with thrombolyis alone, 2.5% in patients with rescue PTCA). In both groups, 23% developed signs of heart failure. There was a trend to more intraventricular thrombus (1.2% vs 0.4%), but fewer incident strokes (0.2% vs 1.3%, p=0.07) in group P. Cumulative 5-day mortality or stroke was 4.9% in Group P vs 6.1% in Group T (p=ns). Using stepwise logistic regression analysis, mode of reperfusion therapy (thrombolysis or PTCA) was not an independent predictor of early outcome. In patients admitted within 6 hours of symptom onset, mortality was 4.7% in patients undergoing primary PTCA, vs 5.0% in patients treated with thrombolysis.
Conclusion: in this large "real world" registry, patients treated with intravenous thrombolysis or primary PTCA have quite similar baseline profiles. More than half of the patients treated with thrombolysis underwent rescue PTCA, which appears a safe procedure (5-day mortality: 2.5%). Early clinical outcome was not different with either mode of reperfusion therapy.

2064 Early ST-segment resolution correlates with myocardial salvage in patients with acute myocardial infarction treated with stenting or thrombolysis

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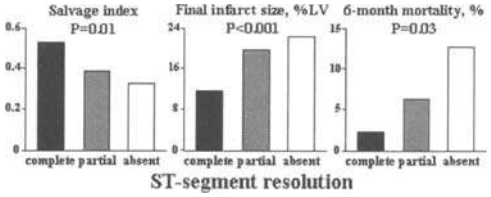
Previous studies have shown that the degree of early ST-segment elevation resolution may predict final infarct size and clinical outcome in patients (pts) with acute myocardial infarction (AMI). Whether this parameter correlates with myocardial salvage determined by scintigraphy remains unknown.
Included in this study were 243 pts with AMI enrolled in the randomized STOPAMI 1&2 trials, which compared stenting with thrombolysis. Serial 12-lead ECGs were performed at baseline and after completing coronary stenting (n=122) or thrombolysis (n=121). ST-segment resolution was defined as complete (>= 70%), partial (< 70% to 30%) and absent (< 30%). Initial perfusion defect (area at risk) was assessed by Tc 99m sestamibi scintigraphy at baseline, final infarct size was assessed by a second scintigraphic study at 7-14 days and salvage index was the proportion of area at risk salvaged by reperfusion.
The ST-segment resolution was complete in 85 pts, partial in 80 pts and absent in 78 pts. The figure clearly shows that a higher degree of ST-segment resolution is associated with a greater salvage index, a smaller infarct size and a lower mortality at 6 months. The association between ST-segment resolution and myocardial salvage remained significant (P<0.01) after adjustment for other covariates. When stenting was compared with thrombolysis, it led to more ST-segment resolution (P<0.001), to a grater salvage index (P<0.001) and to a lower 6-month mortality (P=0.02).
Conclusion: The degree of early ST-segment elevation resolution on surface ECG correlates with myocardial salvage in scintigraphy in pts with AMI after reperfusion therapy. Therefore, ST-segment resolution may serve as a simple and useful means for comparing the efficacy of different reperfusion strategies.



PERCUTANEOUS CORONARY INTERVENTION IN ACUTE CORONARY SYNDROMES

2065 Intracoronary thrombus, distal flow and ischaemic events in non-ST-segment elevation acute coronary syndromes

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Introduction: Thrombus formation on an atherosclerotic plaque is a common finding in ACS. In this study, we correlated the severity of the thrombus with distal flow and adverse clinical outcomes.
Materials and Methods: The 1569 patients in the PRISM-PLUS who had coronary angiography 48 and 96 hours after initiation of antithrombotic therapy were studied. All angiographic data were centrally analyzed. Distal flow assessed by the TIMI flow grade and the corrected TIMI frame count (CTFC), and percent lumen diameter reduction (%LDR) by quantitative angiography.
Results: Thrombi were found in 674 patients (45%), normally distributed around a median of 50%LDR of the underlying plaque, half of them on stenoses 40% to 60%. Total %LDR of culprit lesions was 82% with thrombus and 78% without (NS); thrombi contributed to 31% of LDR, more so on more severe underlying stenoses. CTFC increased sharply with ^{3}75%LDR (slope=2.11) and less so when thrombi were present (slope=1.33). Matched for %LDR, thrombotic lesions had more TIMI grade 3 flow (73.4% vs. 45.7%, p<0.0001 for %LDM ^{3}75%). Death, MI, death/MI, and death/MI/refractory ischemia occurred more frequently with a thrombus (5.71% vs. 3.24%, p=0.034; 8.57% vs. 6.66%, p=0.221; 14.29% vs. 9.9%, p=0.021; 27.14% vs. 18.17%, p<0.0001), but could not be predicted by total % obstructive stenosis, % underlying stenosis, or CTFC.
Conclusions: In ACS thrombi frequently persist despite antithrombotic therapy, and contribute significantly to lumen diameter obstruction and strongly predict ischemic events. The thrombotic component, however, is less flow restrictive than plaques, supporting mechanisms other than flow obstruction to explain thrombi-associated ischemic events.

2066 Beneficial effect of first day PTCA for acute non-ST-segment elevation myocardial Infarction in clinical practice: results of the ACOS registry

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Background: The VINO Study has reported a reduction in mortality and re-infarction by first day angioplasty (PTCA) in patients (pts) with acute coronary syndromes (ACS) without persistent ST-elevation. Data on the outcome of pts with non-ST-elevation myocardial infarction (NSTEMI) in clinical practice do not yet exist.
Methods: Since June 2000 consecutive pts with ACS have been enrolled into the ACOS-Registry (Acute Coronary Syndrome, 154 hospitals) in Germany. We analysed the impact of first day PTCA in patients with NSTEMI on hospital outcome.
Results: Out of 9065 consecutive patients with ACS, 3727 (41%) presented with NSTEMI, 880 of these patients (24%) received first day PTCA. Determinants in favour of first day PTCA were prior PTCA/CABG (OR 2,17; 1,68-2.81), age < 70 years (OR 2,10; 1,80-2,60) and male gender (OR 1,70; 1,31-2,10). Determinants against first day PTCA were diabetes mellitus (OR 0,77; 0,62-0,95) and prior myocardial infarction (OR 0,54; 0,42-0,70).

First day PTCA for NSTEMI

	NSTEMI with First day PTCA	NSTEMI without First day PTCA
n=	880	2847
Age (years)	64	71
Male Gender	78%	62%
Prior MI	16.0%	22.2%
Prior PTCA	18.4%	9.7%
Hypercholesteremia	54.5%	46.7%
Hypertension	66.4%	70.6%
Diabetes	25.0%	33.1%
Hospital mortality	0.9%	7.2%

p<0.01 for all parameters

After adjusting for differences in baseline characteristics and adjunctive therapy, first day PTCA in NSTEMI patients was associated with a 85% reduction of odds for hospital mortality (OR 0.15, 0.06-0.41).
Conclusion: Determinants for first day PTCA in acute NSTEMI were male gender, age < 70 years and prior PTCA or CABG. First day PTCA in acute NSTEMI was associated with a high 85% reduction of adjusted odds for hospital mortality. This high reduction might reflect an additional clinical selection bias for which we could not correct with the available parameters in the multivariate analysis.

2067 Clinical outcome of percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes in catheterisation laboratory without on-site surgical back up

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Background: Percutaneous coronary interventions (PCIs) in patients (pts) with non ST elevation acute coronary syndromes (NSTE ACS) are recognized as interventions with high risk of adverse cardiac events. It could be important for catheterisation laboratories (cath-lab) without on site surgical back up. However, coronary stents and platelet glycoprotein IIb/IIIa receptor inhibitors improve safety of PCIs. The purpose of the study was to analyze the immediate and long term outcome of PCIs performed in cath-lab without on-site surgical back up in pts with NSTE ACS.
Methods: In a cohort of 479 consecutive pts (160 with NSTE ACS - group A, 319 with stable angina - group B) we analyzed short and long-term clinical outcome of PCIs performed in cath-lab located several kilometres from cardiac surgery department with effective transfer time < 30 minutes.
Results: Stent implantation rate (61,3% vs 50,2%; p= 0,04) and frequency of using IIb/IIIa blockers (17,5% vs 6,3%; p<0,001) was higher in group A. In hospital outcome was similar in both groups - A vs B: (death: 0,6 vs 0,6%; myocardial infarction: 2,5 vs 1,6%; urgent rePCI: 1,9 vs 1,3%). Acute PCI complications requiring urgent surgical operation occurred in 1 pt (0,6%) from group A and in 1 pt (0,3%) from group B. Those pts were successfully transferred for cardiac surgery. Kaplan Meier event-free survival was similar in both groups.
Conclusions: In the era of coronary stents and platelet glycoprotein IIb/IIIa receptor inhibitors there was no difference in short and long term outcome of PCIs between pts with NEST ACS and stable angina. The early aggressive approach to pts with ACS was feasible and safe in cath-lab without on site cardiac surgery. Surgical backup was still necessary for only few PCI complications.

2068 Angiographic and clinical outcomes after angioplasty in saphenous vein graft for acute myocardial infarction

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Objective: We compared in-hospital and six months outcomes of patients who underwent a primary percutaneous coronary intervention (PCI) of an acute myocardial infarction (AMI) related to a vein graft obstruction or a native artery.
Methods: From January 1994 to June 2001, 556 patients underwent a primary PCI in the first 24 hours of an AMI. In 52 patients the target vessel was an occluded saphenous vein graft (SVG) and in 504 patients it was a native artery (NA). All of them were prospectively enrolled in the cardiovascular research database. Myocardial infarction was confirmed by documented Creatine Phosphokinase-MB elevation. After discharge, clinical follow-up was performed via regular outpatient review and standardized telephone interview.
Results: There was no difference in patients demographic data between the two groups.In the SVG group the average graft age was 7.2 ± 5.4 years.
Respectively in the SVG group and in the NA group: Intra-aortic balloon pump was used in 29.7% vs. 28.1%, glycoprotein IIb/IIIa inhibitors and thrombolytics were respectively administered in 32.2% vs. 36.1% and 4.7% vs. 2.4%. At the time of the procedure, 43% of the grafts were totally occluded compared to 45% of the vessels in the NA group. During the procedure a distal embolization was observed in 18.6% vs. 4.2% (p<0.05). An Angiographic success (defined as a <50% diameter residual stenosis with TIMI flow grade 3) was obtained in 79,1% in the SVG group vs 91.6% in the NA group (p<0.05). A stent was implanted in 51.7% of SVGs vs. 43.6% of native arteries (p=NS).
In-hospital outcome and follow-up: Respectively in the SVG and NA groups, in-hospital mortality was 4.3% vs.3.1%. At six months, the mortality was 16.1% vs. 10.6% (p = NS) and the TLR-MACE (death, Q wave MI and TLR) was 42.9% vs 23.3% (p = 0.001). At one year, the mortality was 19.6% vs 13.6% (p = NS) and TLR-MACE was 51.1% vs. 29.6% (p = 0.003).
Conclusion: Primary PCI of AMI related to saphenous vein graft occlusion can be successful. Although, these patients are at high risk and have lower angiographic and clinical outcomes compared to patients with an acute infarct angioplasty on native artery.

2069 Primary PTCA in coronary artery bypass vein grafts in patients with acute myocardial infarction

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Percutaneous coronary intervention (PCI) in coronary artery bypass vein grafts has been shown to be associated with more adverse events compared to interventions in native coronary arteries.
Therefore we analyzed the outcome of patients with acute myocardial infarction treated with PCI within 24 hours after symptom onset. All consecutive interventions in 82 hospitals of the ALKK in Germany between 1992 and 2000 were prospectively recorded in a registry. Informations about in-hospital complications including death, re-myocardial infarction, urgent CABG, re-occlusion, and urgent re-PCI were available in more than 98% of the patients. During this period a total of 20,023 interventions were performed in patients with acute myocardial infarction within 24 hours after symptom onset. Of the latter 462 interventions were done in coronary artery bypass vein grafts. The in-hospital mortality rate was 13,8% compared to 8.7% in patients with PCI in native coronary arteries. TIMI 3 flow was achieved in 71,6% in vein grafts compared to 88.5% in native vessels. The use of stents was comparable with 53.1% versus 49.8%. Emergency surgery and re-PCI was necessary in 2.4% and 5.6% of the CABG patients.
Conclusion: Primary PCI in vein grafts in patients with acute myocardial infarction is associated with a lower procedural success rate and an increased in-hospital mortality rate compared to primary PCI in native vessels. Therefore the search for adjunctive therapies to improve outcome in these high risk patient group should be continued.

2070 Protect against reperfusion injury with ITF-1697 in acute myocardial infarction: PARI-MI trial

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Introduction: ITF1697 is a CRP-derived tetrapeptide which increases myocardial perfusion and reduces infarct size in various experimental animal models of ischemia and/or ischemia-reperfusion. It preserves the integrity of microcirculation and inhibits PMNs and platelet adhesion to the endothelium.
Objectives: To assess safety, preliminary efficacy and clinical outcome of prolonged i.v. infusion of ITF1697 in 4 dosages (0.1, 0.5, 1.0 and 2.0 μg/Kg/min),in pts with acute myocardial infarction(MI) eligable for primary PCI.
Methods: This was a randomised, double blind, multicentre, placebo-controlled, pilot, dose finding study.
After inclusion of 50 pts per group, an interim analysis was performed for safety and preliminary efficacy. Based on this analysis, 3 treatments (placebo and two active) were continued up to approx. 100 pts each. Safety was evaluated by incidence of bleeding, death, thrombotic events, serious adverse events (SAEs). Efficacy was measured by improved perfusion (TIMI-flow, TIMI frame count, Blush grade, ST-segment resolution) and reduced myocardial damage (enzymatic infarct size, left ventricular ejection fraction). Clinical outcome was assessed as measured by incidence of death, recurrent MI, recurrent ischemia and SAEs until discharge and 30-day follow-up. Analysis was performed in a central lab. Pts of both sexes with acute MI were enrolled if time from symptom onset was within 12 hrs, ST-segment elevation more than 0.2mV in two or more contiguous leads and sum of ST elevation more than 10mm. Planned use of thrombolytic agents was not allowed. I.V.infusion was started before procedure up to 24 hrs. Pts were followed until 1 month after treatment.
Results: Between Jan. 2001 and Dec. 2001, 11 sites enrolled 402 pts. Interim analysis did not evidence any safety concerns. Baseline characteristics were similar within the groups.
Data entry and statistical analysis is ongoing. Final data will be presented at the ESC meeting in Berlin 2002.

GENETICS OF DILATED CARDIOMYOPATHY

2071 Lamin A/C mutation in a family with dilated cardiomyopathy and conduction disease

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Dilated Cardiomyopathy (DCM) is a heart muscle disease characterized by left or biventricular dilatation and is a frequent cause of heart failure. Probably more than 25% of DCM cases are of familial ethiology. Mutations in the gene for lamin A/C were described for autosomal dominant DCM. We aimed to analyze this gene in a large kindred with DCM.
Methods: A large family comprised of 40 members was evaluated by physical examination, ECG, echocardiography, and heart catheterization according to WHO criteria. DNA was extracted from blood lymphocytes. We screened all 12 coding exons of the lamin A/C gene (LMNA) using polymerase chain reaction and direct automated sequencing with fluorescent dyes.
Results: We report here a three generation family with autosomal dominant familial DCM. In 20 out of 40 family members, we detected a heterozygote deletion of adenine at position 1397 in exon 8 of LMNA. The mutation is predicted to lead to a frameshift with a premature stop codon at position 479 and therefore to a truncated protein. Course and severity of the disease showed a great variability in the group of the family members with the mutation. Disease manifestation in this family began in adolescence with sinus or atrioventricular node dysfunction. Later these individuals showed a mild dilatation of the left ventricle, an impaired systolic function, and malignant tachyarrhythmias. The endstage of the disease manifested clinically as overt congestive heart failure.
Summary: We identified a mutation in the lamin A/C gene (1397delA) in a three generation family with autosomal dominant DCM characterized by ventricular dilatation, impaired systolic function, and conduction disease.

2072 β2-Adrenergic receptor gene polymorphisms are genetic susceptibility factors to idiopathic dilated cardiomyopathy

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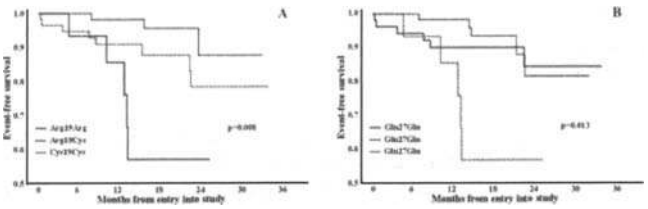
Abnormalities of the beta-adrenergic pathway have been described in idiopathic dilated cardiomyopathy (DCM), some of them related to beta 2-adrenergic receptor (beta 2-AR) polymorphisms. We sought to assess whether functionally relevant polymorphisms in the beta 2-AR gene have a role in favouring DCM susceptibility or in modifying its evolution.
A total of 132 unrelated patients (pts) with DCM (WHO criteria) and 180 unrelated controls were included in an association study. Alleles and genotypes frequencies of the 5'leader cistron (LC) Arg19Cys, Arg16Gly, Gln27Glu, and Thr164Ile polymorphisms in the beta 2-AR gene were compared between pts and controls. The Gly16 allele (68% vs 56%, $p<0.005$) and the Gly16Gly genotype (48% vs 32%, $p<0.02$) frequencies were significantly higher in pts when compared with controls. Linkage disequilibrium among beta 2-AR polymorphisms was observed ($p<0.0001$). The pts were prospectively followed up for a median period of 17 months. Kaplan-Meier survival curves showed that pts who were homozygous for both of the 5'LC-Arg19 and the Glu27 alleles had a significantly higher risk to experience hospitalisation for heart failure (HF) in comparison with those carrying the other genotypes (RR=4.78, $p<0.005$) (Figure). After adjustment for age, NYHA functional class, and left ventricular ejection fraction the predicting value to HF events according to 5'LC-Arg19Arg and Glu27Glu genotypes remained significant with a relative risk of 3.57 ($p<0.05$).



In conclusion, our data show that the Gly16Gly genotype of the beta 2-AR gene confers an increased genetic susceptibility to develop DCM. Moreover, homozigosity for 5'LC-Arg19, Gly16, and Glu27 alleles allows to identify a subgroup of DCM patients at higher risk of HF worsening.

2073 Absence of mutation in 4 candidate genes in a large European population of dilated cardiomyopathy

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Dilated cardiomyopathy (DCM) is a chronic disorder of the heart muscle mainly characterised by ventricular dilatation and impaired systolic function. It is a heritable disorder in 25-30% of the cases, mainly transmitted as an autosomal dominant disease with incomplete penetrance. To date, 9 genes encoding cytoskeletal, contractile and nuclear inner membrane associated protein have been found mutated in this disorder. However, no major gene or mutation responsible for the disease has been identified, each mutation being found at best in a few family only, underlying the genetic heterogeneity of DCM.
As several other morbid genes has to be identified, we have screened a population consisting on 100 independent familial and sporadic cases for mutation in 4 candidate genes potentially involved in DCM: 1) beta-sarcoglycan and delta-sarcoglycan genes, encoding members of the dystrophin-associated protein complex, the later being previously implicated as a morbid gene in DCM and 2) phospholamban and the alpha-B56 subunit of protein phosphatase 2A (PP2AB56alpha) genes encoding proteins involved in the cardiac Ca^{2+} signalling pathway and located in DCM chromosomal loci identified by linkage analysis.
No deleterious mutations have been found in any of the 4 genes by PCR-SSCP and sequencing analysis. Then, in this rather large population of DCM patients, none of these gene could be considered as responsible for the disease.
Three strong candidate genes, beta-sarcoglycan, phospholamban and PP2AB56alpha, have been excluded for a role in familial DCM in our study. However, given the marked heterogeneity observed in familial DCM and the 70-90% power of mutation detection of PCR-SSCP, further screening might be needed on additional subjects before definitive exclusion of these three genes. Finally, this study confirm the previously reported low frequency of mutations in the delta-sarcoglycan gene as disease causing in familial DCM.

2074 Mutational analysis of lamin A/C gene in dilated cardiomyopathy without conduction defect and without skeletal muscular dystrophy

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Aims: About 25% of idiopathic dilated cardiomyopathy (DCM) are familial with a large predominance of autosomal dominant transmission. The lamin A/C (LMNA) gene has been reported in familial DCM associated with conduction-system disease or skeletal muscle dystrophy. However, the involvement of the LMNA gene in patients with DCM without conduction defect and without skeletal muscle dystrophy, which are by far the large majority of cases, is unknown. Therefore, we performed a mutational analysis of the LMNA gene in such families.
Methods: We analysed the coding sequence of the LMNA gene in a Caucasian population of 35 independent probands with familial DCM and 17 sporadic cases, using a systematic PCR/SSCP/Sequencing methodology.
Results: (1) A new mutation (Glu161Lys) was identified in the alpha-helical rod domain of the lamin A/C in one family with a particular phenotype characterised by early atrial fibrillation without (3 among 5 adults) or with (2/5 adults) dilated cardiomyopathy, without conduction defect or skeletal muscle myopathy. (2) No mutation in the LMNA gene was found in other familial or sporadic cases with pure form of DCM. (3) Finally, new polymorphisms in the LMNA gene were identified in this study.
Conclusion: A specific phenotype characterised by early atrial fibrillation with or without DCM is associated for the first time with the LMNA gene. Conversely, mutations in the LMNA gene appear as a rare cause of isolated and classical DCM without significant conduction defect, skeletal muscle dystrophy, or early atrial fibrillation.

2075 A novel lamin A/C mutation (TRP190ARG) associated with familial dilated cardiomyopathy

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Background: Mutations of LMNA A/C gene, encoding lamin A/C, have been identified as causes of familial dilated cardiomyopathy (DCM). Our objective was the identification of LMNA A/C gene mutations in patients with familial DCM.
Methods and Results: After informed consent, genomic DNA of patients with familial DCM and of their relatives was isolated from frozen blood samples and coding regions of lamin A/C gene were PCR amplified, studied by SSCP and cycle sequenced.
A new mutation (Trp190Arg) was identified in exon 3 in two cousins with idiopathic DCM: a male that required cardiac transplant at age 45 years (left ventricular end diastolic diameter (LVEDD) 55 mm, ejection fraction 14%, right ventricular dilatation), and a 46 years old female with dyspnea, LVEDD of 59 mm and ejection fraction of 49%. Both of them had abnormal ECGs with very low voltages. Their mothers had died of cardiac causes in their forties. The Trp190Arg mutation was also present in the 19 years old son of the affected male, who had a normal echocardiography (LVEDD 46 mm, ejection fraction 58%) and a pathologic ECG with left ventricular hypertrophy and repolarization abnormalities. One of the 23 years old twin sons of the affected female, who also carried the mutation, had a normal echocardiography (LVEDD 55 mm with a body surface of 2 m^2, ejection fraction 62%) and a borderline ECG. His twin brother was completely normal. None of the affected patients had conduction system defects, signs of skeletal myopathy or lypodistrophy.
The mutation was confirmed by RFLP with Tha1. It was not present in more than 100 healthy controls and it affects a highly conserved region identical in Xenopus laevis, Gallus gallus, Rattus norvegicus and humans.
Conclusions: The Trp190Arg mutation in exon 3 of the LMNA A/C gene is associated with a severe form of familial DCM. The phenotype of this family suggests an electrocardiographic progression from an initial pattern of left ventricular hypertrophy towards very low voltages in the late stages of the disease.

2076 Mutations in dystrophin and lamins genes in patients with dilated cardiomyopathy

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Background: Mutations of dystrophin gene may cause Becker and Duchenne muscular dystrophy (BMD/DMD) and simultaneously dilated cardiomyopathy (DCM). One of the forms of Emery-Dreifuss muscular dystrophy (EDMD) is autosomal dominant one due to mutations of A/C lamins gene, and these patients may also suffer from AV blocks and/or DCM.
Aim: To detect mutations in genes for dystrophin and A/C lamins in patients with DCM and compare them with neurological and histopathological findings.
Patients and methods: We examined 37 pts with DCM (left ventricular dilatation with ejection fraction below 45%, coronary heart disease and acute myocarditis excluded), age 43.6±9.1 years, LVEF 28.4±8.8%, and 13 pts with permanent pacemakers for AV blocks, age 37.1±12.0 years. Clinical cardiological and neurological examination, electromyography (EMG), and evaluation of m. vastus lateralis biopsy for histology, histochemistry, and imunohistochemistry were performed. Genetic analyses consisted of detection of dystrofin gene mRNA expression from Pm, Pb a Pp promotors by means of reverse transcription, polymerase chain reaction (PCR) and DNA sequence analysis, and of analysis of muscle biopsies for mutations of A/C lamins gene by means of amplificated PCR, denaturating high-performance liquid chromatography (DHPLC) and sequence analysis.
Results: Neurological clinical signs of myopathy were found in 3 pts, EMG had myogenic picture in 20 pts, myogenic finding in muscle biopsy was detected in 8 pts. Genetic analyses: we found mRNA transcript from Pm promotor with deletion of exon 2 in 1 pt, mRNA transcript from Pb promotor with insertion of a part of the first intron in 1 pt, and mRNA transcript from Pm promotor with deletion of exon 3 and parts of exons 2 and 4 in 1 patient. Two mutations of A/C lamin gene were detected: in 1 pt with DCM and in 1 pt with pacemaker.
Conclusion: We detected mutations in dystrofin and lamins genes in several patients with DCM or AV blocks. It seems useful to broaden the spectrum of examinations for mutations of other cell proteins, to evaluate also relatives of our patients and to create the register of patients with DCM, BMD/DMD and EDMD in our area.

RESULTS FROM RECENT CLINICAL TRIALS: IMPLICATIONS FOR DRUG THERAPY IN PRACTICE

2077 Does carvedilol prevent and reverse cardiac cachexia in patients with severe heart failure? Results of the COPERNICUS study

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In end-stage heart failure (HF), cachexia is common, is associated with increased morbidity, and fails to respond to conventional therapy. In a prespecified analysis of the COPERNICUS trial, we evaluated the impact of body mass index (BMI) on survival and the effects of placebo (PBO) and carvedilol (CRV) on the development of cachexia (weight loss => 6% during follow-up) in 2262 patients with no baseline edema.
There was a highly significant decrease in mortality with increasing BMI ($P<0.0001$). For each 1.0 unit increase in BMI, the risk of death decreased by 7.7%. Annual mortality rates for PBO and CRV in each BMI category are shown in the table. Baseline values for BMI did not influence the benefits of CRV on survival (P=0.97).

	Annual PBO mortality rate	Annual CRV mortality rate
BMI < 22 (n=279)	29.4%	20.8%
BMI 22 to < 25 (n=567)	25.2%	18.4%
BMI 25 to < 30 (n=932)	19.4%	10.3%
BMI => 30 (n=484)	8.0%	6.7%

During follow-up, 14.1% of PBO patients and 10.2% of CRV patients developed cachexia (P=0.005). CRV (but not PBO) patients showed a significant increase in weight, which was not related to fluid retention. Mean changes in weight in the CRV and PBO groups were +0.5 vs -0.1 kg (P=0.0002) after 4 months, +0.9 vs -0.1 kg (P<0.0001) after 8 months, and +1.1 vs +0.2 kg (P<0.0002) after 12 months of maintenance therapy.
Conclusion: In severe HF, CRV increases body weight and reduces the incidence of new cachexia. Given the association of body mass and survival, prevention and reversal of cachexia may contribute to the benefits of CRV in patients with severe HF.

2078 Betablockers use in severe and old patients with heart failure. Data from BRING-UP 2 study

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Objective: To analyze the change in betablockers use in severe patients with heart failure (HF), and in those aged 70 years and more, before and after the COPERNICUS study.
Method: We compared the rate of prescription of BB in the BRING-UP 1 study (Betablockers in patients with congestive heart failure. Guided use in clinical practice) (year 1998-1999) and in the BRING-UP 2. These studies are observational, multicentric and have the aim to monitor and implement BB use in HF pts over the whole Italian Country. While BRING-UP 1 focussed the attention on all out-patient with HF and was conducted before the presentation of the COPERNICUS results, BRING-UP 2 has the aim to evaluate the applicability, the safety profile and the associated outcome of BB treatment in specific soubgroup of patients with HF, for whom there was evidence of undertreatment with BB (pts in NYHA class III and IV and patients aged 70 years or more).
Results: The results reported in the table show the rate (a) of patients already on treatment at the baseline visit of the two studies, (b) of those in whom treatment was started and (c) of those for whom the BB treatment was not prescribed.

Table: Use of betablockers in BRING-UP 1 and 2

	BRING-UP 1 NYHA III-IV (1063 pts)	BRING-UP 2 NYHA III-IV (1267 pts)
Already on betablockers	19%	33%
Started on betablockers	23%	30%
No betablockers p<0.001	58%	37%
	BRING-UP 1 (pts >70 years: 1024)	BRING-UP 2 (pts >70 years: 1529)
Already on betablockers	18%	33%
Started on betablockers	21%	28%
No betablockers p<0.001	61%	39%

Conclusion: In the last two years, in Italy significant increase in BB use in out-patients with severe heart failure and in the older age vas observed. This relevant changes could be due (a) to the intensive educational and research programs adopted by the National Societies of Cardiologist, and (b) by the results of RCTS, such as COPERNICUS, which seem to be well accepted and incorporated in real world clinical practice.

2079 Prescription of betablockers in patients with heart failure in different clinical settings: data from the TEMISTOCLE study

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Background: The survival benefit due to beta-blocker treatment in patients with heart failure (HF) has been established by recent trials. However, the current use of this treatment in clinical practice is not well know.
Aims: To compare the rate of prescription at hospital discharge of beta-blockers in patients admitted for HF in Internal Medicines (IM) or in Cardiology (C) Departments.
Methods and Results: From 14 to 25 February 2000 baseline data from 2127 patients with CHF referred to 417 hospitals (250 IM and 167 C) were collected. Even if C prescribe beta-blockers more frequently than IM (17.8%. and 8.7%, p<.001), the largest part of the study population (82.9%) was not prescribed on beta-blockers. Table shows main contraindications and/or adverse reactions due to beta-blockers.

	IM (%)	C (%)
COPD	41.0	35.9
Diabetes	7.1	3.6
PVD	1.6	1.0
AVB >=2° or HR <50 BPM	2.4	6.0
Hypotension	4.5	12.0

A large number of patients were not prescribed on beta-blockers because of advanced age and HF severity. Among the different betablocker agents, carvedilol was the most used in both settings (76.0% in IM and 77.4% in C), followed by metoprolol (9.0% in C vs 6.4% in IM) and by atenolol (9.2% in IM vs 3.0% in C). For 12.2% of the pts (10.0% in IM vs 16.3% in C), there were no specific reasons for not prescribing betablockers.
Conclusions: The rate of patients treated with beta-blockers is rather low, particularly in patients admitted to IM. Age and advanced HF were still considered by participating doctors uncertain indications. Nationwide programs to narrow the gap between research and practice should be implemented.

2080 Randomised, double-blind, placebo-controlled study of carvedilol in heart transplant candidates: results from the EFICAT-multicenter-trial

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Background: In patients with severe heart failure (CHF) and in heart transplant candidates (HTC) the COPERNICUS- and EFICAT-Trial showed improvement of survival and pump function with Carvedilol (C). It remained to be analysed, however, whether the effect of C on ejection fraction (EF) depends on CHF etiology and, whether C influences left ventricular (LV) remodelling in HTC.
Methods: The study was designed as a randomised, double-blind, placebo(P)-controlled trial and conducted in 3 German transplant centers. Study duration was 12 months. HTC with cardiomegaly and advanced LV systolic dysfunction were eligible. Endpoints were the absolute changes from baseline to the latest available measurements of LVEF (radionuclide ventriculography) and LV end-diastolic and endsystolic dimensions (EDD, ESD, echocardiography), respectively, in C- and P-treated HTC.
Results: The trial prospectively randomized 118 HTC with end stage CHF of ischemic (I, n=44) or non-ischemic (NI, n=74) etiology, a mean ± SD (median) age of 53.3±9.8 (55.5) years and a mean LVEF at baseline of 19.9±6.6 (20.1)% with a change of +6.0±9.3 (+3.9)% in the C-treated and +0.7±7.1 (0.0)% in the P-treated group (p<0.008, Wilcoxon two-sided test). In the subgroups, the change in LVEF was in HTC-I +5.2±7.0 (+4.0)% in the C-treated vs. -5.3±6.8 (-5.5)% in the P-treated group (p<0.03); in HTC-NI the change in LVEF was +9.9±11.6 (+8.0) % in the C-treated vs. +2.7±7.6 (0.0)% in the P-treated group (p<0.04). The mean EDD and ESD at baseline were 73.8±8.2 (74.0)mm and 64.7±9.0 (64.0) mm in the C-treated and 75.8±9.1 (74.0) and 66.3±10.0 (66.5)mm in the P-treated group (all NS), with a change of -0.9±7.6 (-1.0) and -3.7±8.9(-2.5)mm in the C-treated and of +1.8±6.9 (1.0) and +0.1±7.4 (-1.0) mm in the P-treated group. In the subgroups, the changes in EDD were in HTC-I +2.3±8.6 (+1.0)mm in the C-treated and +4.3±6.3 (+4.0)mm in the P-treated group, in HTC-NI -3.0±6.2 (-3.0)mm in the C-treated and +1.1±7.1 (+1.0)mm in the P-treated group. The changes in ESD were in HTC-I +0.4±9.7 (0.0)mm in the C-treated and +2.7±8.6 (+2.0)mm in the P-treated group, in HTC-NI -6.1±7.5 (-5.0)mm in the C-treated and -1.2±7.3 (-2.0)mm in the P-treated group.
Conclusion: Even in HTC with end stage heart disease pharmacological therapy with C improves significantly LVEF over a prolonged period of time irrespective of CHF etiology. While the decrease in mean ESD probably reflects improved LV performance, the concomitant decrease in mean EDD observed only in HTC with NI-CHF suggests that reverse remodelling might be inducible by C-treatment.

2081 Effect of carvedilol on mortality and reinfarction in left ventricular dysfunction after infarction. A subgroup analysis from CAPRICORN study

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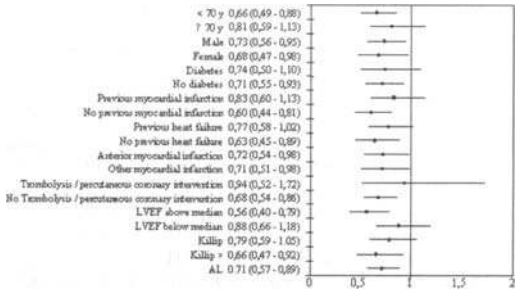
The long term clinical efficacy of carvedilol in patients with left ventricular dysfunction following acute myocardial infarction (AMI) was investigated in a double-blind randomised placebo controlled trial. 1959 patients with AMI and left ventricular ejection fraction (LVEF) of < 40% were included in 163 centres in 17 countries and randomly assigned to receive either carvedilol or placebo. 47% were treated with thrombolytics or primary percutaneous interventions and 97% with ACE inhibitors. Mortality or nonfatal reinfarction was analysed in subgroups by demographics, previous history and clinical profile of the patients.
Findings Carvedilol reduced all cause mortality by 23%, HR 0.77 (95% CI 0.60–0.98), p = 0.03 and non fatal myocardial infarctions by 41%, HR 0.59 (0.39 – 0.90), p = 0.01 and all cause mortality or non fatal MI by 29%, HR 0.71 (0.57 – 0.89), p = 0.002. The analysis showed a consistent positive trend in the reduction of reinfarction and all cause mortality or reinfarction in all subgroups by age, gender, previous history of diabetes, infarction, or heart failure, AMI location, revascularisation therapy, LVEF, and Killip class (Figure).



Mortality and reinfarction HR (95% CI).

Conclusions Carvedilol reduces mortality and nonfatal reinfarction in patients with left ventricular dysfunction or failure after AMI. Consistent positive trends were observed in all subgroups.

2082 Efficacy and safety of carvedilol in patients with low systolic blood pressure in the COPERNICUS study

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Background: Since survival trials with metoprolol and bisoprolol excluded patients with a systolic blood pressure (SBP) < 100 mm Hg, many physicians are reluctant to use beta-blockers in such patients, especially those with a vasodilatory effect.
Methods: We evaluated the effects of carvedilol (CRV) vs placebo (PBO) in 2289 patients with severe heart failure (HF) in the COPERNICUS study, of whom 132 had a SBP < 96 mm Hg and 264 had a SBP of 96-105 mm Hg at the time of randomization. Following initiation of treatment, SBP increased (CRV>PBO) in the patients with low SBP and fell transiently (CRV>PBO) in the patients with higher SBP.

	All-cause Mortality		Death or HF Hospitalization	
	1-year PBO rate	Hazard ratio (CRV:PBO)	1-year PBO rate	Hazard ratio (CRV:PBO)
< 96 mm Hg	34%	0.77	61%	0.74
96 - 105 mm Hg	25%	0.61	43%	0.75
106 - 115 mm Hg	18%	0.65	37%	0.78
116 - 125 mm Hg	17%	0.61	40%	0.54
> 125 mm Hg	15%	0.60	32%	0.68

Results (see table): Patients with low baseline SBP were at extremely high risk of a major clinical event, the magnitude of risk decreasing with increasing SBP. However, CRV decreased the risk of death and of death or HF hospitalization in all SBP subgroups, the magnitude of benefit being independent of SBP (interaction P=0.64 and P=0.80 for mortality and for death or HF hospitalization, respectively). The rate of permanent withdrawal decreased with increasing baseline SBP (P=0.0001), similarly for PBO and CRV (interaction P=0.25). Hypotension was reported as an adverse effect more with CRV than PBO overall; this difference was not accentuated in the low SBP subgroups.
Conclusions: These results provide the first evidence that CRV is effective and well tolerated in patients with severe HF and a low SBP.

FROM PERFUSION ASSESSMENT TO CLINICAL DECISION MAKING: THE ROLE OF CONTRAST ECHOCARDIOGRAPHY

2099 Is myocardial perfusion by echocardiography useful to select patients with chest pain for an early discharge in the emergency department?

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Background: We previously showed that myocardial perfusion is accurately assessed by Adenosine Contrast Echocardiography (ACE) with PESDA in pts with stable coronary artery disease (CAD). However its utility for pts undergoing a rapid evaluation for possible ischemia in a Chest Pain Center (CPC) has not yet been evaluated. Accordingly, we assessed the ability of ACE to determine the perfusion patterns of these pts to identify those with low-risk CAD for an early and safe discharge.
Methods: 75 pts (53 male, 59±14, 28-90 years) were admitted to a CPC to investigate possible ischemia due to CAD. First ECG and initial CK-MB were non-diagnostic. According to the chest pain characteristics 3 groups were formed: A- typical angina: 11 pts; B- suggestive of angina: 33 pts; and C- non-suggestive of angina: 31 pts. ACE with triggered (1:1) 2nd harmonic imaging, was visually assessed (2 independent investigators), at rest and after IV injection of adenosine (ADN), using PESDA, continuously infused at 1-2ml/min. Myocardial perfusion was defined as normal (negative for ischemia) or abnormal (reversible or fixed defects-positive). Coronary angiography (ANG) was obtained in 27 pts (in 11/11, 12/33 and 4/31 pts from groups A, B, and C respectively) within 48 hours from ACE. For each patient 3 LV territories (related to right coronary, circumflex and left anterior descending arteries) were considered.
Results: 81 territories were analyzed in pts with ANG with 33 related to coronary artery with obstruction >75% (all but one with abnormal perfusion); and 48 territories supplied by normal or no flow limiting (<75%) coronary artery (46 with normal perfusion). The sensitivity was 97%, the specificity was 95.8% and the global accuracy was 96.3%. Regarding to the 48 pts with no ANG, ACE was negative in 42 (15 and 27 in groups B and C respectively) that were discharged within 48 hours, and positive in 6 (all in group B) that were moved to a Coronary Care Unit for additional investigation.
Conclusion: ACE with PESDA is an accurate method to study myocardial perfusion in pts admitted to a CPC to elucidate the etiology of a chest pain providing useful informations for a safe and early discharge.

2100 Feasibility and diagnostic accuracy of real-time myocardial contrast echocardiography in detecting stress-induced perfusion defects

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Background: Real-time myocardial contrast echocardiography (MCE) is discussed as a useful adjunct to stress testing but little is known about its feasibility and diagnostic accuracy.
Aim: We tested agreement between real-time Power Pulse Inversion imaging and 99mTc-Sestamibi-SPECT in evaluating myocardial perfusion on a segmental level. Methods: MCE (Optison, 8-10 ml/h) was performed at rest and during peak dipyridamole stress in 70 unselected patients (mean age: 63+9 years; 54m, 16f, 25 anterior-, 10 inferior-, and 11 lateral infarcts, 10 single-,32 multi vessel disease) with angiographically proven coronary artery disease undergoing SPECT imaging for clinical reasons. From apical four- and two chamber views and comparable SPECT views, 12 myocardial segments were scored for regional opacification/uptake by two pairs of blinded observers (0= absent, 1= mildly reduced, 2 = severely reduced, 3= normal). Ischemic segments by either method were defined as the difference of 1 grade between stress and rest images. 4 patients were excluded from the study due to really poor echographic window.
Results: Of 792 analysed segments 143 were inadequate for reading by MCE, mostly confined to basal segments. Interobserver variability was good (kappa=0,76). Overall agreement between the two methods was poor (59%, kappa=0,25) when including unreadable segments but good (82%, kappa=0,63) when excluding those segments. Highest concordance was found in apico-lateral (85%) and the lowest in basals segments (18%). Concordance between the methods was higher for diagnosing fixed defects (72%) and normal perfusion (88%), than for diagnosing reversible defects (65%). Conclusion: This study demonstrates that real-time MCE can detect perfusion defects during pharmacological stress and agrees reasonably well with 99mTc-Sestamibi-SPECT. However, diagnostic feasibility is limited in basal segments and caution should be exerted when diagnosing stress induced ischemia.

2101 Time course of improvement of microvascular perfusion and contractile function after successful reperfusion of acute myocardial infarction

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We sought to investigate the time course of changes of microvascular perfusion and contractile function within the risk area (defined as segments with wall motion abnormality before reperfusion therapy) in patients with first acute myocardial infarction (AMI) before and after successful reperfusion therapy using venous myocardial contrast echocardiography (VMCE).
Methods: VMCE (3ml Optison in 27ml NaCl, 200ml/h, intermittent harmonic imaging, 4- and 2-chamber views (six segments each), off-line digital image processing) was performed in 49 patients (male n=42, median age 57 years) with AMI (infarct related artery (IRA): LAD n=20, RCA n=21, LCX n=8; CK max. 837±663 U/l) before and 3 hours, 14 days and 6 months after reperfusion therapy (percutaneous coronary intervention n=45, thrombolysis n=4). Videointensity (VI) of each risk area segment was normalized to the VI of the brightest normokinetic segment of the same view. Echocardiographic evaluation of contractile function (semiquantitative wall motion score) at rest was performed simultaneously with VMCE. Repeat coronary angiography was performed at day 14 in all 49 patients and in 45/49 patients after six months.
Results: Reperfusion therapy was successful in all patients. TIMI 3 flow was present in all patients at day 14 and after six months. Myocardial contractile function was initially abnormal in 200 of a total of 488 segments. The table shows normalized VI (%) and the wall motion score (WMS) of risk area segments (n=200)over time.

VI and WMS values over time

	Before reperfusion	After reperfusion	Day 14	Six month
VI %	40*(±26)	60 (±30)	65 (±32)	68 (±32)
WMS	2.87 (±0.34)	2.84 (±0.39)	2.26* (±0.87)	2.02* (±0.9)

(mean±SD; * indicates significant difference ($p<0.05$) compared to all other values in the same row)

Conclusions: In patients with successful reperfusion therapy of acute myocardial infarction, the main improvement of myocradial microvascular perfusion occurs immediately after reperfusion whereas recovery of contractile function is a prolonged process.

2102 Improved prediction of myocardial viability by contrast echo in dobutamine non-responsive myocardium early after acute myocardial infarction

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Background: Prediction of myocardial viability in the infarct related myocardium has important therapeutic prognostic and implications. Dobutamine response of viable but dysfunctional segments may be prevented by critical stenosis of infarct related artery. Thus dobutamine echocardiography (DE) may underestimate the prediction of myocardial viability. We hypothesised that presence of microvascular integrity, detected by myocardial contrast echocardiography (MCE) in dobutamine non-responsive segments may enhance identification of myocardial viability.
Methods: Accordingly, 98 pts underwent low dose DE and intravenous MCE (Optison) on the same day, 3-5 days after acute myocardial infarction (AMI). Akinetic segments were assessed for dobutamine response, contrast opacification and recovery of function 6m after AMI (standard reference for myocardial viability).
Results: There were a total of 421 akinetic segments of which 111 segments recovered function at 6m. Of these, 45 segments did not show any dobutamine response. On the other hand, contrast opacification was present in 21 (47%) of these 45 dobutamine non-responsive segments. Sensitivity of DE for prediction of recovery of function was 59%. When contrast opacification was seen in the dobutamine non-responsive segments, sensitivity improved to 81% ($p<0.01$ compared to DE alone). The only independent predictor of recovery of dysynergic myocardium was the combination of DE and MCE.
Conclusion: In conclusion, MCE enhances detection of myocardial viability in dobutamine non-responsive segments early after AMI.

2103 Does real time perfusion during stress echocardiography increase the detection of viable myocardium?

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Background: Assessment of reversibility and viability in patients with resting wall motion abnormalities during Dobutamine Stress Echocardiography (DSE) may not be easy. However, availability of myocardial perfusion techniques and detection of perfusion by quantitative analysis may identify reversible or viable segments more accurately.
Methods: Therefore, we studied seventy-nine patients with contrast Dobutamine Stress Echocardiography, either with intermittent triggered or real time perfusion. All patients had nuclear (sestimibi or thallium SPECT) and coronary angiograms. Patients were divided into three groups, based on presence of reversible or fixed defect or viability using nuclear. Wall thickening and perfusion analysis were performed. Ratio of normal wall thickness to abnormal was compared at base (WTRb) and peak (WTRp). Similarly ratio of perfusion in normal and infarcted regions were calculated at base (MPAb) and peak (MPAp).
Result: See Table. Sensitivity in the detection of viability increased from 52% to 62% (P=0.06) when quantitative perfusion analysis is added to visual innterpretation. Similarly there was a trend for higher accuracy for reversibilty with perfusion when compared to conventional visual interpretation(76% vs 69%, p=NS).

	WTRb	WTRp	MPAb	MPAp
Fixed	3.8	7.7	2.3	3.3
Viable	3.6	6.2	2.2	2.4
Reversible	3.7	11.4*	2.3	10.9*
P	NS	*0.05	NS	*0.001

Conclusion: Perfusion ratio is a sensitive marker for detecting viability and reversibility. Overall additive information derived from perfusion in conjunction with visual interpretation increases detection of reversible and viable segments in clinical setting of resting wall motion abnormality.

2104 Prediction of left ventricular remodelling in patients with acute myocardial infarction: role of intravenous myocardial contrast echocardiography

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Background: The development of left ventricular (LV) remodeling is crucial in patient (pt) outcome after an acute myocardial infarction (AMI). The extent of microvascular perfusion has been shown to predict the ultimate amount of myocardial damage and the extent of residual viability, which can favorably condition pt prognosis, by preventing LV remodeling.
Aim of this study was to assess the role of intravenous myocardial contrast echocardiography (IVMCE) in the prediction of LV remodeling in patients (pts) with AMI.
Methods: Seventy-two pts with AMI, successfully treated with acute PTCA, underwent IVMCE and low-dose dobutamine echocardiography (LDDE) during hospital admission but at least 3 days after AMI (4.9±1.1 days). IVMCE was performed with Levovist (4 gr) with Harmonic Power Doppler Imaging, with an end systolic triggering 1:4 cardiac cycle. IVMCE was graded semiquantitatively on a score of 0 (no visible contrast effect), 0.5 (patchy contrast enhancement) and 1 (homogenous contrast effect). Pts were considered to have microvascular impairment (IVMCE-), if < 50% of segments within the infarct related area had score 1. A mean perfusion score index (PSI) was calculated for each pt by averaging the contrast scores in the area at risk. At six-month follow-up a new echocardiogram was performed. Pts were also followed-up for the occurrence of adverse cardiac events (cardiac death, reinfarction, malignant ventricular arrythmia, congestive heart failure, target lesion revascularization) for 6 months.
Results: Sixty-three pts (55 male; 56±10 yrs) completed the study. Pts with a good perfusion at IVMCE (IVMCE+) showed a lower CK peak ($P<0.001$) and CK MB ($P<0.01$), a better wall motion score index (WMSI; 1.62±0.2 vs 1.86±0.2; $P<0.0001$) and a higher amount of myocardial viability at LDDE (-0.34±0.2 vs -0.22±0.2; $P<0.05$) compared with IVMCE- pts. At follow-up, a higher improvement in WMSI (-0.30±0.21 vs -0.07±0.3 $P<0.001$) was observed in IVMCE+ pts, while IVMCE- pts showed a higher incidence of adverse cardiac events (64% vs 22%; $P<0.005$) and an evident increase in LV end diastolic volume (EDV) from baseline to six-month follow-up (99±10 vs 136±26 ml; $P<0.0001$), implying LV remodeling. The results of canonical correlation analysis showed that PSI was significantly correlated to the variation of LVEDV ($r2 = 0.33$; $P=0.0001$). By stepwise multiple regression analysis, microvascular impairment at IVMCE was a significant independent predictor of LV remodeling ($P<0.0001$).
Conclusions: IVMCE seems to be an important diagnostic tool, able to early predict LV remodeling in pts with AMI.

IMPROVED ASSESSMENT OF MYOCARDIAL ISCHAEMIA BY TISSUE DOPPLER

2105 Tissue Doppler echocardiography and strain Doppler echocardiography: a head-to-head comparison in moderate and severe ischaemia

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Background: Tissue Doppler echocardiography (TDE) and Strain Doppler echocardiography (SDE) are noninvasive methods for measuring myocardial velocities and deformation, respectively. We compared the ability of the two methods to identify myocardial dysfunction during different degrees of ischaemia.
Methods: In 7 anaesthetized dogs we measured longitudinal myocardial velocities by TDE, strain by SDE, and dimensions by sonomicrometry. Flow in the left anterior descending coronary artery (LAD) was reduced by 57 ± 8% and 100%, and sonomicrometry in the LV anterior wall showed regional hypokinesis and dyskinesis, respectively (Table).
Results: (see table below)
During severe ischaemia TDE showed marked changes in IVC and IVR velocities, and Vsys2 reversed, consistent with dyskinesis (Table). Similarly, SDE showed systolic lengthening and marked post-systolic shortening. During LAD stenosis, which caused moderate hypokinesis there were only minor reductions in TDE velocities, and there was overlap with velocities in non-ischemic myocardium. However, SDE showed marked decrease in systolic strain and substantial post-systolic shortening, and this contractile pattern clearly identified ischemic myocardium.
Conclusion: During severe ischaemia both TDE and SDE identified dyskinetic myocardium. However, in hypokinetic myocardium velocities by TDE showed substantial overlap with values in non-ischemic myocardium, while SDE clearly distinguished ischaemic from non-ischemic regions. Therefore SDE appears to be more sensitive than TDE in identifying myocardium with moderate ischaemic dysfunction.

2106 Post-systolic shortening during dobutamine stress echocardiography: delayed contraction of viable dyssynergic myocardium

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Background: Dobutamine stress echocardiography (DSE) interpretation remains limited by its subjective assessment of wall motion score during stress. Pulsed wave-tissue Doppler imaging (PW-TDI)-derived ejection phase (EP) and post-systolic shortening (PSS) velocities may help to render DSE objective.
Objectives: We evaluated the additional value of dobutamine challenge on both EP and PSS velocities to identify dysfunctional, but viable myocardial segments using F18-fluorodeoxyglucose(FDG)-SPECT as an independent reference.
Methods: 40 patients (26 males, mean age 57 ± 9 years) with ischemic severe left ventricular dysfunction (mean ejection fraction: 33 ± 10%) underwent DSE with PW-TDI. The six-segment model (posterior, anterior septum, lateral, inferior, anterior and posterior walls) of longitudinal contraction was used for PW-TDI at rest, low dose of dobutamine (10 μg/kg/min) and peak stress. EP and PSS velocities were analysed off-line. EP/PSS ratio was calculated. The optimal cut-off levels of myocardial velocity values for the assessment of myocardial viability were calculated by ROC-curves analysis. Myocardial viability by wall motion score during DSE was assessed if 2/3 of the segment showed a biphasic, sustained improvement or ischemic response. Viability by FDG-SPECT was assessed if 2/3 of the segment showed a normal or mildly reduced FDG uptake.
Results: out of 240 segments, resting severe dyssynergy was present in 168 (70%) segments. Myocardial viability in 61 (36%) segments by DSE and in 78 (46%) by FDG-SPECT. The agreement between PSS and DSE for myocardial viability was 65%, kappa 0.30 compared to 79%, kappa 0.59 for PSS vs FDG-SPECT. As compared to DSE, EP with PSS improved sensitivity for myocardial viability to 98% vs 79%, $p < 0.01$. Similarly, EP/PSS ratio at low dose of dobutamine improved sensitivity for myocardial viability: 96%. Cut-off values of PSS vs viability by FDG-SPECT were >5 cm/s at rest and >6 cm/s at low dose of dobutamine. Cut-off values of EP/PSS ratio vs viability by FDG-SPECT were >0.8 at rest and >0.3 at low dose.
Conclusions: The presence of PSS and a more sustained increase of PSS velocities during DSE were able to predict viable myocardium. EP and PSS improved DSE accuracy to recognize myocardial viability. PSS appears clinically confirming the delayed active contraction of dyssynergic myocardium.

Abstract 2105 – Table

Anterior Wall	V Ivc-neg (cm/s)	V Sys1 (cm/s)	V Sys2 (cm/s)	V Ivr-neg (cm/s)	SS by strain (%)	PSS by strain (%)	SS by crystals (%)	PSS by crystals (%)
Baseline	-1.4 ± 0.7	2.7 ± 0.9	1.4 ± 0.7	0.6 ± 0.4	12.6 ± 2.5	0.6 ± 0.6	11.2 ± 3.1	1.0 ± 0.5
LAD - stenosis	-2.0 ± 0.9	2.1 ± 0.5	0.8 ± 0.3 *	1.1 ± 0.6 *	6.7 ± 3.0 *	5.7 ± 0.7 *	6.6 ±2.9 *	5.7 ± 2.2 *
LAD - occlusion	-4.6 ± 2.0 *	1.4 ± 0.4 *	-0.3 ± 0.5 *	2.5 ± 0.8 *	- 8.1 ± 3.4 *	8.4 ± 2.1 *	- 5.6 ± 2.5 *	8.4 ± 2.4 *

V Ivc = Peak negative velocity in the isovolumetric contraction period, V Sys1= Peak systolic velocity, V Sys2 = mid systolic velocity, V Ivr = Peak positive velocity in the isovolumetric relaxation period, SS=peak systolic shortening, PSS=post-systolic shortening. Mean ± SD. * $p < 0.05$.

2107 Myocardial elasticity by strain Doppler echocardiography – A method to identify viable myocardium

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Introduction: Myocardium that has undergone irreversible ischaemic damage is characterized by tissue oedema and therefore a decrease in elasticity. We hypothesized that strain Doppler echocardiography (SDE) may be used to assess myocardial elasticity, and thereby identify viable myocardium.
Methods: In 5 anaesthetized dogs we measured LV pressure, myocardial long axis strain by SDE, and segment lengths by sonomicrometry. Ischaemia was induced by LAD occlusion and haemodynamic measurements were done repeatedly for 4 hours. Infarcted myocardium was identified by TTC-staining and myocardial oedema by dry/wet weight ratio. Systolic elasticity (compliance) was calculated as systolic lengthening by sonomicrometry divided by systolic pressure rise.
Results: During LAD occlusion the ischaemic segment became dyskinetic with systolic lengthening and post-systolic shortening (PSS). In each experiment TTC-staining indicated irreversible myocardial injury after 4 hours of ischaemia, and the dry weight/wet weight ratio was reduced by 16.0 ± 3.8% (± SEM, $p<0.05$) indicating myocardial oedema. Systolic lengthening and PSS decreased during the ischaemic period from 10 ± 1% to 6 ± 1% ($p<0.05$) and from 10 ± 1% to 5 ± 1% ($p<0.05$), respectively (fig. 1). Systolic lengthening and PSS correlated well with myocardial elasticity (fig. 2). Strains by SDE correlated well with strains by sonomicrometry ($r = 0.58$, $p<0.01$).

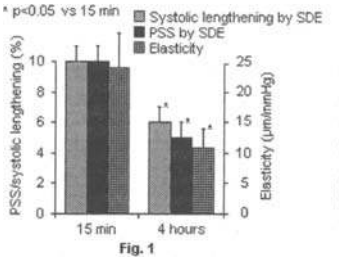

Fig. 1

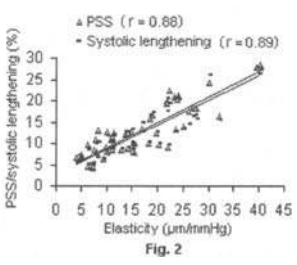

Fig. 2

Conclusions: The development of irreversible ischaemic myocardial injury is characterized by a decrease in systolic lengthening and PSS. This reflects decreased myocardial elasticity caused by tissue oedema. Thus, assessment of elasticity by SDE may help to determine if dyskinetic myocardium is viable.

2108 Impact of regional ischaemia on Doppler myocardial imaging parameters of left ventricular function during differing inotropic conditions

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Background: Recently, ultrasound based measurements of strain rate (by Doppler Myocardial Imaging (DMI)) have been shown to reflect regional myocardial contractility under various conditions of inotropic states. The following study evaluates the impact of different inotropic stimulation on myocardial function during normal perfusion and ischemia.
Methods and results: Six minipigs underwent complete anaesthesia and mechanical ventilation. A conductance catheter was placed into the left ventricle (LV) to obtain maximal endsystolic elastance (Ees) and dp/dtmax as the first derivative of LV pressure over time. An active coronary perfusion catheter was positioned in the proximal part of the coronary circumflex artery and blood for active perfusion was withdrawn from the femoral artery. DMI studies were done using a parasternal long axis view taking the posterior left ventricular wall as the region of interest. The following parameters were measured at baseline, after administration of dobutamine (10 µg/kg bodyweight) and esmolol (1-2.5 mg/kg bodyweight): Peak systolic strainrate (SR; unit 1/s), maximal endsystolic elastance (Ees) and dp/dtmax. After inducing regional myocardial ischemia by reducing the coronary blood flow to 7 ml/min the above mentioned measurements were repeated.
During normal coronary perfusion Ees and SR showed a significant correlation ($r=0.81$; $p < 0.001$). SR increased significantly after dobutamine administration and decreased after beta-blockade (4.8±0.8 vs 8.5±1.8 and 3.0±0.6). During regional ischemia SR was significantly reduced at baseline (4.8±0.8 vs 3.0±0.9), after dobutamine (8.5±1.8 vs 3.6±1.6) and after esmolol infusion3.0±1.6 vs 1.9±0.4) compared with each of these inotropic states at normal coronary perfusion. During ischemia there was a non-significant increase in SR after dobutamine and a significant decay after beta-blockade compared to baseline measurements (3.0±0.9 vs 3.6±1.6 and 1.9±0.4). Dp/dtmax and Ees as markers of global left ventricular function did not change due to regional ischemia.

	basel/np	dobu/np	esmo/np	basel/isch	dobu/isch	esmo/isch
strainrate	4.8 (0.8)*	8.5 (1.8)#*	3.0 (0.6)#*	3.0 (0.9)	3.6 (1.6)	1.9 (0.4)#
elastance	7.5 (3.4)	22.1 (12.5)#	5.1 (1.6)	9.8 (4.5)	11.5 (5.5)	7.4 (4.5)
dp/dtmax	1847 (222)	5053 (1108)#	1299 (186)#	2048 (329)	4346 (703)	1031 (107)

Conclusion: SR reflects myocardial contractility well during normal perfusion. After regional ischemia, dobutamine failed to increase SR but esmolol administration lead to a decay of SR. Therefore, SR might still detect subtle changes of regional function in severely ischemic myocardium.

2109 Can strain rate echocardiography measure changes in local left ventricular function following pharmacologic inhibition of myocyte energetics?

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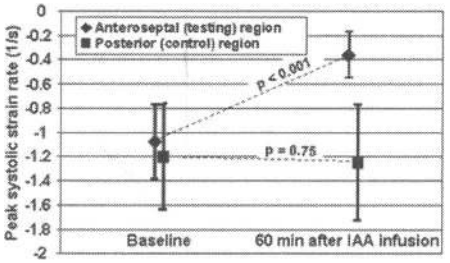
Background: We developed a pig model of non-ischemic inhibition of myocyte energetics using selective coronary administration of iodoacetamide (IAA). IAA inhibits creatine kinase (CK) and glyceraldehyde phosphate dehydrogenase (GADPH), which leads to cessation of cross-bridge cycling and uncouples myocardial contraction. We hypothesized that inhibition of regional myocardial energetics by IAA should decrease regional peak systolic strain rate, a measure of contractility, in the area at "metabolic" risk.
Methods: We administered 1 mg/kg of IAA via intracoronary catheter into a mid segment of the left anterior descending coronary artery in 15 pigs. Preservation of myocardial perfusion was verified by contrast echocardiography. Myocardial strain rates derived from tissue Doppler data were measured in the apical septal region at baseline and during a fully developed metabolic stress, ie, 60 minutes following IAA administration. Mid-posterior region served as a control. Myocardial biopsies for assessment of CK and GADPH activities in the apical septal region were obtained at baseline and 60 minutes after IAA administration to document metabolic inhibition.
Results: Peak systolic strain rates significantly decreased in the (IAA-affected) anteroseptal region but not in the (control) mid-posterior region (Figure). The local change in peak systolic strain rates was associated with a drop of CK and GADPH activities to <10% of the baseline value.



Conclusions: Functional effect of local pharmacologic inhibition of myocyte energy metabolism can be measured by quantitative analysis of regional contraction rates using strain rate echocardiography.

2110 Prognostic value of myocardial velocity gradient in patients with dilated cardiomyopathy: a tissue Doppler imaging study

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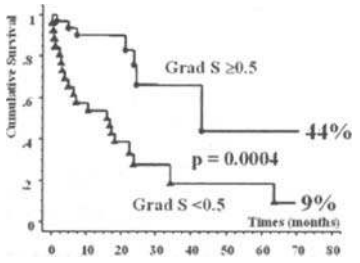
Tissue Doppler imaging (TDI) allows assessment of regional myocardial function by measuring deformation parameters such as velocity gradient between endocardium and epicardium (Grad, s^{-1}). To assess the prognostic value of systolic Grad in patients (Pts) with heart failure, we prospectively analyzed 70 Pts (53±12 yrs) with idiopathic dilated cardiomyopathy (DCM) by conventionnal echo-Doppler and TDI. NYHA class was II in 24 Pts, III in 24 and IV in 22. Mean left ventricular ejection fraction (EF) was 29±12%. Mean peak VO2 was 17±5 ml/mn/kg. Systolic Grad was measured within the posterior wall (mean value: 0.9±0.9s^{-1}).
During follow-up (20±16 months), major cardiac events occurred in 28 pts: 14 hospitalisations for worsening heart failure (11 leading to heart transplantation), 10 cardiac deaths, 4 ventricular tachycardia.
At univariate analysis, NYHA IV, peak VO2 < 16 ml/mn/kg, systolic pulmonary artery pressure > 35 mmHg, cardiac index < 2.7 l/mn/kg and systolic Grad < 0.5 were significantly predictive of cardiac events (figure: Kaplan-Meier analyses of cumulative rates of survival (%) in Pts stratified into 2 groups on the basis of systolic Grad value).
Multivariate logistic regression analysis (Cox model) revealed an independent predictive value of only two parameters: VO2max and systolic Grad.



Conclusion: In patients with DCM, regional myocardial function assessment by TDI is predictive of long term survival and might add useful information for clinical decision-making for cardiac transplantation.

COMPUTER DEMONSTRATION

2119 Implementing national guidelines on risk prediction and primary prevention of coronary heart disease in a cardiology information system

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Purpose: The Dutch Institute for Healthcare Improvement (CBO) recently published a national consensus concerning both risk prediction and guidelines for primary prevention of coronary heart disease (CHD). The risk prediction charts for CHD and cardiac vascular disease (CVD) need manual operation and therefore its use during clinical routine is time-consuming. This paper presents an easy to use implementation of the CBO guideline in a large academic medical center.
Methods: The guideline is based on a risk prediction algorithm published in 1991 by the Framingham group. This nonproportional hazards Weibull accelerated failure time model was taken as an input for a Delphi based application, as part of the Cardiology Information System (CARIS) which was developed by the department of Cardiology, LUMC. The implemented risk factors are gender, age, systolic blood pressure, ratio of total cholesterol and HDL cholesterol, smoking and diabetes. The advanced programming environment makes it possible to evaluate also other prediction models, such as a Cox proportional hazards model.
Results: By selecting the patient, automatically the absolute risks on CHD and CVD are calculated and an advice is presented whether or not to treat the patient's bloodpressure or cholesterol. All parameters that are available in CARIS are filled in automatically. The remaining items are imported from the Hospital Information System. The application runs on a standard Windows-2000 PC. Routinely, the system is connected to the Hospital Information System, but for demonstration purposes it can also run as a stand-alone application. In clinical practice both the Weibull and the Cox models resulted in similar treatment advises.
Conclusions: Since no manual input is necessary, the risk estimation tool is quick and easy to use. Furthermore, patients can be shown how changes in lifestyle may effect their risk profile. At this moment the effect of the prediction tool is subject of further study. The tool will soon be also available on the LUMC-Cardiology website.

2120 A new computer-assisted fuzzy logic based approach in assessing the probability of significant coronary artery disease

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Introduction: Due to the limited availability of coronary angiography facilities in some Eastern European countries we propose a new method, with better diagnostic performances than ECG treadmill test (TM), which can become a useful tool in selecting patients before invasive and expensive investigations. Fuzzy logic is a new and promising approach in the field of computer-assisted decision making. In this study, we tested the performance of a newly developed software in assessing the probability of significant coronary artery disease (CAD).
Methods: Based on the principles of fuzzy logic, we designed a program to calculate the individual probability of having relevant CAD. Risk factors, ECG treadmill test results and echo measurements at rest were weighted and processed according to fuzzy logic and not to binary logic rules. The Centre-of-Area- (COA) and the Mean-of-Maxims-Method (MOM) were used for defuzzification. To test the performance of the algorithm, we studied prospectively 152 patients (mean age 54±19years, 60 female, 92 male) with clinical suspicion of CAD. All patients underwent 99Tc-Sestamibi SPECT perfusion imaging, or coronary angiography, or both. We considered significant CAD in those cases with reversible defects at scintigraphy, or more than 50% coronary stenoses at coronary angiography. The program's output and the result provided by the classic TM alone were compared, for each patient, to the scintigraphic and/or angiographic diagnosis. Sensitivity(SENS), specificity(SPEC), positive and negative predictive values (PPV and NPV) were calculated.
Results: An or-linked combination of the defuzzification methods (COA or MOM) performed best. SENS of the algorithm vas cosiderably higher than classical TM (81% vs. 58%), with no major decrease of SPEC (SPEC 76% vs. 80%). Accordingly, PPV changed from 81% to 83% and NPV from 57% to 73%.
Conclusion: Our data show, that a computer-assisted processing of easily accessible basic patient data substantially improves the diagnosis accuracy of significant CAD and thus, reduces the need for invasive examinations.

POSTER DISPLAY IV

MODERATED POSTER SESSION IV

P2121 Inhibition of platelet activation in congestive heart failure by selective aldosterone receptor antagonism and angiotensin-converting enzyme inhibition

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Background: Increased risk of thrombembolic events in congestive heart failure (CHF) has been attributed to a hypercoagulable state including vascular endothelial dysfunction and platelet activation. The role of the activated renin-angiotensin-aldosterone system (RAAS) for platelet activation in CHF is currently unknown.
Methods and Results: After experimental myocardial infarction (MI), male Wistar rats were treated with placebo, the ACE inhibitor trandolapril (TR, 0.3mg/kg body weight/day), the selective aldosterone receptor antagonist eplerenone (EPL, 100mg/kg/day) or the combination of both (TR-EPL) for 10 weeks. Platelet-bound fibrinogen and surface-expressed P-selectin were not modulated in MI rats with LVEDP<15mmHg (10.9±0.6, and 19.3±3.5 mfu [mean fluorescence units]) compared with sham-operated animals (9.9±0.8, and 20.1±2.3 mfu), while they were significantly increased in CHF rats (LVEDP>15mmHg, 15.2±1.0, and 65.5±1.1 mfu, $p<0.001$ vs. sham-operation and MI). TR treatment significantly reduced platelet P-selectin expression while bound fibrinogen was not modulated. EPL reduced P-selectin expression to a comparable extent, while platelet-bound fibrinogen was normalized (10.2±1.2 mfu, $p<0.001$). A combination of EPL and TR even normalized P-selectin expression. Beneficial modulation of platelet activation by TR-EPL treatment was associated with the normalization of acetylcholine-induced, endothelial-dependent relaxation of rat aorta, and basal phosphorylation of the vasodilator-stimulated phosphoprotein (VASP). In contrast, treatment with TR or EPL alone was only partially effective.
Conclusions: Platelet activation was evident only in rats with severe CHF. Only the complete RAAS blockade with eplerenone and trandolapril normalized increased platelet activation presumably by improvement of endothelial-dependent NO-bioavailability leading to the normalization of decreased basal VASP phosphorylation, a key regulator of the initial sequences of platelet inhibition.

P2122 Improvement in acute treatment of myocardial infarction in clinical practice 1994-2001 resulted in a 28% reduction of hospital mortality

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Background: The results of randomised trials showing the beneficial effect of reperfusion and adjunctive therapy on clinical outcome of patients (pts) with ST-elevation myocardial infarction (STEMI) had been implemented into the guidelines for the treatment of STEMI. It is unknown if therapy of STEMI changed in clinical practice and if these changes were associated with an improvement in outcome after STEMI.
Methods: Since 1994 consecutive pts with AMI have been enrolled into three large German AMI-registries to document pts characteristics, acute treatment and clinical outcome of AMI: MITRA (Maximal Individual Therapy of AMI) and MIR (Myocardial Infarction Registry) 1994–2000 at 271 hospitals and ACOS (Acute Coronary Syndrome Registry) since 2000 at 154 hospitals. A total of 97 hospitals participated in MITRA and MIR as well as in ACOS. Acute reperfusion and adjunctive treatment and the hospital mortality of STEMI were compared between the 2-year periods beginning with 1994 until 2001.
Results: Between 1994 and 2001 a total of 11802 consecutive pts with AMI were enrolled into the AMI-registries in these 97 hospitals.
Conclusion: Between 1994 and 2001 the acute treatment of STEMI in clinical practice in Germany significantly improved according to existing guidelines. This improvement in acute therapy was associated with a 28% decrease in hospital mortality of STEMI in Germany.

Improvement in therapy and outcome

Time-Period	1994-1995	1996-1997	1998-1999	2000-2001
n=	2070	5070	3174	1488
Age (years)	66	67	67	66
Men	68%	66%	68%	69%
Diabetes	20,7%	22,1%	23,1%	26,4%
Thrombolysis	49,8%	43,5%	39,8%	26,6%
Primary PTCA	8,8%	11,5%	23,1%	30,9%
Aspirin	93,3%	91,6%	94,4%	91,5%
Beta Blockers	49,4%	58,0%	70,7%	79,8%
ACE-Inhibitors	44,6%	57,7%	67,8%	65,3%
Statins	<10%	<10%	53,5%	66,7%
Hosptital Mortality	15,3%	14,5%	13,8%	11,0%

Mortality: p for trend <0,001

P2123 Improvement of ventricular remodelling in rats with CHF: comparative and combined effects of aldosterone receptor blockade and angiotensin-converting enzyme inhibition

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The non-selective mineralocorticoid receptor antagonist spironolactone reduces mortality in patients with severe congestive heart failure (CHF), however its use is limited by considerable side effects. We investigated the effect of the selective mineralocorticoid receptor antagonist eplerenone alone and in co-administration with an ACE-inhibitor on hemodynamics and cardiac remodeling in rats with CHF after extensive myocardial infarction (MI). Rats were treated with placebo (P), the aldosterone receptor antagonist eplerenone (E, 100mg/kg/d), the ACE inhibitor trandolapril (T, 0.3mg/kg/d), or a combination of both for 9 weeks, starting ten days after coronary artery ligation. Left ventricular end-diastolic volume (LVEDV) was obtained by miniaturized impedance/micromanometer catheter (SPR-774, Millar Instruments).
Infarct size were similar among the experimental groups (MI size %: P CHF, 54.5±0.9; E CHF, 54.7±1.0; T CHF, 54.3±2.2; E+T CHF, 54.3±1.6). Despite comparable effects on LV systolic pressure [LVSP (mmHg): Sham, 138±3; P CHF, 110±3[1]; E CHF, 113±5[1]; T CHF, 112±1[1]; E+T CHF, 105±3[1]], the addition of the selective aldosterone receptor antagonist eplerenone to ACE inhibition significantly improved LV systolic [dP/dtmax (mmHg/s): Sham, 12371±375; P CHF, 7316±230[1]; E CHF, 8193±468[1]; T CHF, 8231±401[1]; E+T CHF, 8295±271[1 2]] and diastolic function [dP/dtmin (mmHg/s): Sham, 9614±419; P CHF, 4779±214[1]; E CHF, 5237±283[1]; T CHF, 5277±510[1]; E+T CHF, 5699±311[1 2]] and reduced LV end-diastolic pressure [LVEDP (mmHg): Sham, 4±0.5; P CHF, 21.8±2[1]; E CHF, 15.4±3[1]; T CHF, 16.9±4[1]; E+T CHF, 11.4±2[2]]. In addition, the combination of eplerenone and trandolapril prevented LV dilation [LVEDV (µl): Sham, 530±22; P CHF, 1150±97[1]; E CHF, 859±99[1 2]; T CHF, 890±61[1 2]; E+T CHF, 685±61[3]] and reduced right ventricular hypertrophy [RV/BW (mg/g): Sham, 0.49±0.01; P CHF, 1.13±0.05[1]; E CHF, 0.92±0.06[1 2];T CHF, 0.89±0.06[1 2]; E+T CHF, 0.71±0.05[1 3]] more effectively than either monotherapy. These data suggest synergistic improvement of cardiac failure by long-term aldosterone and ACE inhibition after MI.
(n=7-19) [1]$p<0.05$ vs. sham; [2]$p<0.05$, [3]$p<0.01$ vs. P CHF

P2124 N-acetylocysteine and fibrinolytic therapy for acute myocardial infarction: its influence on plasma chemotactic activity and C5a levels

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Background: Polymorphonuclear neutrophils are attracted into the area of reperfused myocardium and participate in reperfusion injury. It has been demonstrated that administration of n-acetylocysteine (n-ACC) in combination with streptokinase (STK) significantly diminished oxidative stress and improve ejection fraction in patients with acute myocardial infarction.
Methods: The aim of our study was to evaluate the influence of n-ACC on plasma chemotactic activity and C5a plasma levels, in patients with acute myocardial infarction (AMI). 29 patients with AMI were included in the study (22 men, 7 women, mean age 53 yrs). After randomization, n-ACC (or normal saline) infusion was started at 20 mg/min i.v. for 1 hr and 10 mg/min for 23 hrs. Ten minutes after starting of n-ACC infusion 1.5 mln units of STK was given. Peripheral blood was collected before starting of treatment and after 6, 12, 24 and 48 hrs. Plasma chemotactic activity was assessed with the use of modified Boyden chamber method. Control PMNs isolated from healthy subjects were used. Complement C5a plasma levels were assessed by the ELISA method (Enzygnost C5a micro, Behring).
Results: plasma obtained from patients with acute myocardial infarction significantly enhanced chemotaxis of control PMN (chemotactic index 0 hr 2.9±0.3, 6hrs 7.2±0.3, 12hrs 5.6±0.7, 24 hrs 5.2±0.5, 48 hrs 4.9±0.5, p=0.005, p=0.0003, p=0.0003, p=0.002, respectively), n-ACC infusion was associated with significantly diminished plasma chemotactic activity in blood samples obtained after 12, 24 and 48 hrs (p=0.04, p=0.03, p=0.01 respectively). C5a plasma levels were significantly increased, after 6hrs, in comparison to initial value, in patients treated with saline infusion (p=0.02), while there were no significant increase in C5a concentration in patients treated with n-ACC. Plasma isolated from patients treated with saline showed significant increase of C5a over the background level after 6, 12 and 24 hrs in comparison with blood isolated from n-ACC treated subjects.
Conclusions: n-ACC infusion in addition to STK treatment in patients with acute myocardial infarction is associated with diminished plasma chemotactic activity and lower C5a plasma levels.

P2125 The Euroheart failure survey: symptoms and quality of life

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Background: Quality of life (QoL) is reported to be markedly impaired in heart failure and symptoms are often poorly controlled. However, quality of life and symptom severity have rarely been assessed in epidemiologically-representative populations of patients with heart failure.
Aims: To describe the self-assessed QoL of patients with heart failure in a large, international cohort of patients recently (12 weeks) discharged from hospital with a suspected diagnosis of heart failure using the EuroHeart failure QoL instrument.
Methods: The EuroHeart Failure survey included >11,000 patients with a suspected diagnosis of heart failure during a hospital admission. 25 countries belonging to the ESC participated. Surviving patients were invited to attend for interview 12 weeks after discharge at which time they were asked questions about their health, completed the symptom & QoL questionnaire (containing 35 questions with a 6-7 point rating-scale), had a brief physical examination and had a blood sample for BNP measurement taken. A reference population without known disease (UK only; N = 245, mean age 73 years) also completed the questionnaire.
Results: The reference population (mean age 73 years) rated their health as very good or good in 77% of cases (no patient rated themselves less than average) and their overall QoL as very good or good in 86% of cases (1% rated QoL as less than average). The reference population reported very little (<10% of cases) limitation due to breathlessness. The mean age of patients was 71 years (range 63 years in Hungary to 77 years in Sweden) and 48% were women. 45% were reported to have moderate or severe left ventricular dysfunction. 14% of patients died prior to the 12 week follow up visit. From a preliminary sample of 3,249 patients who completed follow-up, 1,444 cases of 'definite' heart failure were identified. One third of these patients reported breathlessness at rest or waking them from sleep while 78% continued to experience breathlessness limiting activities of daily living. Patients rated their health and QoL as poor in 40%and 35% of cases respectively and good or very good in only 11% and 20% of cases respectively. For all of the above variables there was a significant association between HF status and rating (alpha <.05).
Conclusions: Amongst patients who survive 12 weeks after discharge from hospital with a diagnosis of heart failure, troublesome symptoms remain common and patients perception of their quality of life is often poor.

P2126 Are heart failure patients in general practice receiving evidence-based pharmacotherapy?

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Background: Internationally research indicates that pharmacotherapy for chronic heart failure (CHF) is sub-optimal. However, assessment of drug use in heart failure has traditionally focused on the use of individual agents without taking CHF severity into account. This study investigates investigate the pharmacological treatment of CHF in general practice with respect to the available evidence, incorporating both disease severity and the use of combination drug therapy.
Design: Cross-sectional survey
Setting: Dutch General Practice
Participants: 769 CHF patients participating in the IMPROVEMENT of HF study.
Outcomes: For each NYHA severity classification the minimum treatment each patient could expect, appropriate for their NYHA severity classification according to the scientific evidence available at the time of the study (1999) was defined. The proportion of patients receiving, at least, the minimum evidence-based regime per NYHA severity class was determined.
Results: The proportion of patients treated with each drug group increased with increasing CHF severity classification, with the exception of the beta-blockers. With respect to the current evidence, the proportion of patients receiving the minimum evidence-based regime suitable for their severity class decreased as NYHA severity class increased. After adjusting for age and sex, patients with less severe heart failure (NYHA classes 1 and 2) were four to eight times more likely to receive evidence-based treatment than those with more severe heart failure (NYHA class 3 and 4).
Discussion: This study indicates that many heart failure patients in general practice are not receiving evidence-based care when disease severity and combination drug therapy are taken into account. While prescribing of ACE inhibitors appeared adequate, prescribing of beta-blockers was low and indicates an area needing attention. Educational efforts aimed at the improvement of heart failure treatment in general practice are needed, with special consideration given to the role of beta-blockers in the treatment of heart failure.

P2127 Prognostic significance of heart rate variability among the patients with optimized beta-blocking medication after myocardial infarction

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Background: A large body of data has documented that various indices of heart rate variability (HRV) may predict subsequent mortality of the patients after an acute myocardial infarction (AMI). In none of these studies the cardiac medication has been optimized, e.g. 10-40% of the patients have been on beta-blocking (BB) medication. This study assessed the prognostic significance of various measures of HRV among a consecutive series of patients with an AMI in whom the cardiac medication was optimized according to contemporary guidelines.
Patients and methods: Traditional time and frequency domain measures along with the newer fractal measures of HRV were measured in 600 patients after the AMI. Predefined cutoff points for abnormal HRV measures were used. Cardiac medication was optimized with special emphasis on the BB therapy, which was used by 97% of the patients. The end-point was cardiac mortality.
Results: During the mean follow-up of 40±12 months, there were 45 cardiac deaths (7.5%). In univariate analysis, reduced standard deviation of N-N intervals(SDNN<70 msec)(p<0.01), ultra low frequency(lnULF<8,45)(p<0.05) and very-low frequency spectral component (lnVLF<5.30)(p<0.01), short-term fractal exponent (alfa1<0.65)(p<0.001), and long-term fractal exponent (beeta<-1.55)(p<0.001) predicted the subsequent cardiac death. In the multivariate Cox proportional hazards analysis by adjusting for age, diabetes and functional class, the reduced alfa1 remained as the only HRV variable that still predicted the cardiac death (hazards ratio 2.65, 95% CI from 1.37 to 5.13, p<0.01).
Conclusion: Most of the HRV indices retain their prognostic power among the patients with optimized BB therapy after AMI. However, after adjusting for clinical variables, altered short-term fractal exponent was the only HRV variable that still provided prognostic information.

P2128 Heart rate variability in hospitalized patients with decompensated heart failure predicts short-tem survival after discharge

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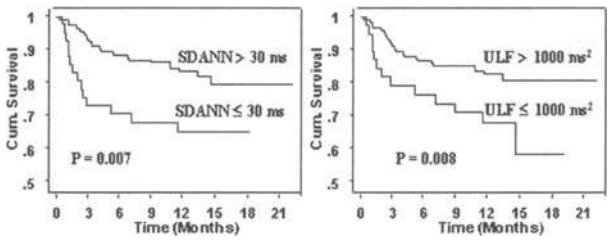
Introduction: Analysis of heart rate variability (HRV) has been used to study autonomic function in patients (pts) with heart failure (HF), and provides information on the risk of death in stable, ambulant pts. With progression from mildly symptomatic HF to decompensated HF, additional progressive autonomic dysfunction occurs. However, the relation between HRV and prognosis in the setting of decompensated HF requiring hospitalization is not known.
Methods: We studied 199 pts (131 men, age 60 ± 14 y) with previous HF, NYHA class III or IV, who were admitted to the hospital for acutely decompensated HF. Twenty-four hour Holter recordings were performed during hospital stay, and HRV parameters were calculated in the time and frequency domain. Cox proportional-hazards model was performed with the following covariates: age, gender, HF etiology, NYHA class, diabetes, sodium (Na) and creatinine levels, presence of ventricular tachycardia, and drug therapies.
Results: During follow-up of 312 ± 150 days, 40 pts (20.1%) died. In Cox's univariate analysis, predictors of death were Na < 132 mEq/L (p = 0.001), creatinine > 2.0 mg/dl (p = 0.034), and the following HRV measures: SDNN (p = 0.045), SDANN (p = 0.009), TP (p = 0.025), and ULF (p = 0.009). In multivariate analysis, SDANN (p = 0.006, RR = 2.7, 95% CI 1.3-5.6), TP (p = 0.01, RR = 2.5, 95% CI 1.2-5.0) and ULF (p = 0.007, RR = 2.6, 95% CI 1.3-5.3) were found to predict survival independently. SDANN and ULF dichotomized at 30 ms and 1000 ms^2, respectively, were the best predictors of mortality (Figure).



Kaplan-Meier survival curves.

Conclusion: The severity of autonomic perturbations during hospitalization for HF decompensation, as reflected by depressed HRV parameters, is a powerful indicator of short-term survival after discharge.

P2129 Effects of sertraline on platelet/endothelial biomarkers in depressed patients after acute coronary events

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Background: Platelets could represent a missing link between incidence of depression and adverse clinical outcomes in patients after acute cardiovascular syndromes (ACS). However, it is still not clear how modern therapies of mood disorders including selective serotonin reuptake inhibitors (SSRI's) affect platelet function in such patients. We serially assessed release of established platelet/endothelial biomarkers in patients receiving sertraline versus placebo in a frame of the SADHART trial.
Methods: Plasma samples (baseline, week 6, and week 16) were collected from 5 sites in the US and Canada from patients treated with Zoloft (n=28), and placebo (n=36). Aspirin and clopidogrel were allowed in this study. Platelet factor 4 (PF4), beta-thromboglobulin (beta-TG), platelet/endothelial cell adhesion molecule-1 (PECAM-1), P-selectin, thromboxane (TxB2), prostacyclin (6-keto-PGF1a), vascular cell adhesion molecule–1 (VCAM-1), and E-selectin were measured by ELISA.
Results: At every time point after baseline for each biomarker measured, patients undergoing treatment with sertraline exhibited substantially less platelet activation than those receiving placebo. These differences reached statistical significance for PF4 (p=0.03), and beta-TG (p=0.04) at week 4, and for beta-TG (p=0.02), PECAM-1 (p=0.01), and P-selectin (p=0.02) at week 16 after randomization. There was a trend towards inhibition of prostanoids (TxB2, and 6-keto-PGF1a), and endothelial-released adhesion molecules (VCAM-1, and E-selectin) in patients treated with sertraline as well, although these changes were not significant.
Conclusion: Despite aggressive anti-platelet regimens including aspirin and clopidogrel, treatment with sertraline in depressed post-ACS patients is associated with the decreased release of platelet/endothelial biomarkers. Mild antiplatelet properties of SSRI's may represent an attractive additional advantage for using these agents in patients with coronary artery disease and ischemic stroke.

CELLULAR ELECTROPHYSIOLOGY

P2130 Regional differences in Na-Ca exchanger current density underlie a regional propensity to arrhythmogenesis

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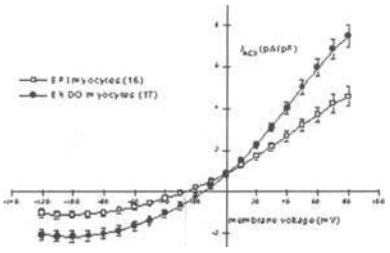
The Na-Ca exchanger current (INCX) contributes significantly to the transient inward current (Iti), which underlies delayed afterdepolarizations. We have measured transmural INCX density and assessed the regional propensity to arrhythmogenesis.
Methods: Myocytes were isolated from basal sub-endocardial (ENDO), mid-myocardial (MID) and sub-epicardial (EPI) regions of guinea-pig left ventricle. Membrane current was measured using the whole-cell patch-clamp technique at 35±1°C. INCX was elicited by a descending ramp protocol (+80 mV to -120mV) under selective conditions and assessed as the Ni-sensitive current. Arrhythmic behaviour was induced by a prolonged step depolarization to +60mV from -40mV after a series of 20 pre-conditioning pulses. Data are presented as mean±SEM (n).
Results: INCX density was significantly greater in ENDO than in EPI myocytes in both 'forward' (-120 to -30mV) and 'reverse' (+20 to +80mV) modes, ($p<0.001$, see fig.). The time to onset of arrhythmia was shorter ($p<0.001$) and the amplitude of Iti was greater ($p<0.05$) in ENDO (n=22) than in EPI (n=24) myocytes. In the presence of thapsigargin (1μM), which inhibits Ca^{2+} re-uptake into the sarcoplasmic reticulum, arrhythmias were abolished although Ca^{2+} flux via the NCX was still greater in ENDO myocytes.



Regional differences in INCX density.

Conclusion: INCX density is greater in ENDO than in EPI myocytes. This may contribute to both the prolonged action potential and to the greater propensity to arrhythmogenesis observed in ENDO rather than in EPI myocytes. In heart failure, INCX is upregulated, hence the sub-endocardial region may be the origin of potentially lethal arrhythmias.

P2131 Block of human IKur and Ito potassium channels by the new antiarrhythmic drug AVE 0118

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The pharmacological treatment of supraventricular tachyarrhythmias, especially atrial fibrillation, is limited by the proarrhythmic potential of currently available drugs. It has been suggested that blockers of the ultrarapid delayed rectifier potassium current IKur might have little proarrhythmic side effects in the ventricle, as the functional channel is only expressed on the atrial level in human heart. Antiarrhythmic drugs that primarily act via block of IKur are not available at the moment. We present the pharmaocolical profile of a new compound AVE 0118 which has been shown to selectively delay repolarization in pig atrium.

Methods: Measurement of IKur, Ito and IK1 in isolated human atrial myocytes and of Kv1.5, expressed in CHO cells, by the use of patch clamp techniques. Kv4.3, HERG, KvLQT1/minK were expressed in Xenopus oocytes and currents recorded by two electrode voltage clamp.

Results: AVE 0118 was a potent blocker of IKur in human atrial cells with an EC50 of 14.4 nM. Kv1.5 channels in CHO cells were inhibited with an EC50 averaging 0.9 μM. Ito was also affected by AVE 0118, 10 μM decreased Ito peak current by 27 ± 8% and strongly altered kinetic properties of the current. The inactivation time constant was markedly shortened, from 33.6 ± 1.8 ms (control) to 11.5 ± 0.9 ms (AVE 0118), which lead to a strong decrease of the calculated net Ito current. Block of Kv4.3 showed similar characteristics to that of Ito. IK1 was only mildly blocked by high concentrations of AVE 0118 (-19.6% at 10 μM AVE 0118). HERG and KvLQT1/minK were not altered by AVE 0118.

Conclusions: AVE 0118 is a highly potent blocker of IKur in human atrium, it also affects Ito in higher concentrations. With a predominant block of IKur, the drug should delay repolarization mainly on the atrial level in human heart. This makes it a class III antiarrhythmic drug with a novel mechanism of action that could be beneficial for the treatment of supraventricular tachycardias, especially atrial fibrillation.

P2132 Altered calcium handling in a rabbit model of left ventricular dysfunction – implications for contractile function and arrhythmogenesis

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Background: Calcium (Ca) has a central role in the mechanical and electrical properties of cardiac myocytes. We investigated changes in cellular calcium handling in a rabbit infarct model of heart failure (8 weeks after coronary artery ligation) which exhibits left ventricular dysfunction, pulmonary and hepatic congestion and a propensity to arrhythmias.

Methods: Voltage clamp studies were performed at 37°C on enzymatically-isolated single cells, loaded with the Ca indicator Fura-2. Sodium-calcium exchanger (NCX) activity was estimated from the rate constant (RC) of Ca decay during 10 mM caffeine application. Sarcoplasmic reticulum Ca pump (SERCA) function was estimated from the RC of Ca decay after brief caffeine application in the presence of 10 mM Ni. SR Ca content was determined from the integral of the NCX current induced by caffeine application. These measures were each performed after 30 sec of 1 Hz stimulation and were corrected for non-NCX Ca removal mechanisms. NCX current density was determined from the Ni-sensitive current in response to a ramp protocol, with major interfering currents blocked and intracellular Ca buffered to 258 nM. Current density data were well fit by the model of NCX function of Weber et al (J Gen Physiol 2001; 117:119-131), which was used to determine V-Max. Allosteric regulation of NCX was studied by examining the outward NCX current through a range of Ca concentrations, using a voltage step protocol.

Results: Compared to sham-operated controls, in LVD cells the decay of the calcium transient was slowed (RC = 2.60±0.17 vs 3.46±0.31/s, p=0.01), there was reduced NCX current density (V-Max = 7.69±0.57 vs 12.19±0.56 A/F, p<0.0001) and reduced NCX activity (0.72±0.07 vs 1.29±0.13/s, p=0.0002). There was a significant increase in SR Ca content (80.58±5.94 vs 66.26±4.07 μmoles/l cell volume, p=0.03) and a trend towards reduced SERCA function (2.02±0.18 vs 2.46±0.32/s, p=0.12). Studies of allosteric regulation of NCX by Ca showed that in LVD cells the exchanger was more sensitive to Ca (Km for calcium activation 206±42 vs 375±62 nM, p=0.02).

Conclusions: Calcium handling is significantly affected in this model of LVD. The balance between NCX and SERCA activity is altered, such that diastolic relaxation is impaired, whilst SR Ca load is increased. These changes could increase the frequency of arrhythmogenic spontaneous Ca release. There is also evidence of altered regulation of NCX.

P2133 B3-subunits isoforms in the human myocardium have different effects on the single pore-forming subunit CaV1.2a of cardiac calcium channels

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Introduction: Voltage dependent L-type calcium channels are multi-subunit membrane proteins which are formed by the ion conducting pore (a1c-), and auxiliary subunits (b, a2d). b-subunits, in particular, have been shown to increase the activity of the pore subunit. In the human heart 3 different b-subunits genes are identified that encode the b1-, the b2- and the b3-subunit. In this study effects of the b2-subunit and two different b3-isoforms (b3a- and a truncated b3-isoform) on the poreforming subunit CaV1.2a are characterised.

Methods and Results: Using sequence specific oligonucleotide primers, a 1252bp full-length cDNA was cloned from non-failing human left ventricular myocardium which is identical to the b3a-subunit from a human thyroidoma cell line. Interestingly, a b3-splice variant was identified that does not contain the 20 nucleotide long exon 6 and results in a premature stop of transcription at nucleotide 632. In non-failing human heart expression of the full length b3a-isoform prevails (83/17%) but changes to 51/49% in the failing human heart. Furthermore, transcript sizes in non-failing/failing myocardium vary with respect to localization: left ventricle 3,5/3,5 kb, right ventricle of 3,2kb/- and right atrium of 3,2/3,5 kb. PCR experiments show that the different transcript sizes are due to variations in the untranslated region. For co-transfection experiments a CHO-cell line already stably transfected with the CaV1.2a of the rabbit L-type calcium channel was used. After cotransfection of a2d-1 and GFP together with either rabbit b2a-, b3a- or the truncated b3-form, fluorescent cells were studied at 24-72 h intervals. Expression of b3a- and the truncated b3-isoform resulted in increased availability of single channels (89,9±5,5%; 76,2±6,7%) compared to cotransfections without b-subunits (31,1±12,6%). In cells cotransfected with b2a, calcium channel availability was unchanged but open probability (12,4±6,3% vs. 0,63±0,21%), mean open time (0,4±0,05 ms vs. 0,18±0,03 ms) and ensemblage average current (174±74 fA vs. 10±1 fA) were increased compared to controls.

Summary and conclusions:

Because effects of both b3-subunit isoforms are rather similar, isoform shift in heart failure has no functional consequence. The b2a-subunit has the most pronounced effect on fast gating parameters, whereas b3-subunits take effect predominantly on the calcium channel availability but not on gating parameters.

P2134 Human atrial Na^+-K^+ pump current, and its sensitivity to voltage or extracellular K^+

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Introduction: The Na^+-K^+ pump is electrogenic and the pump current, Ip, contributes to the cardiac resting and action potential. However, Ip has not been recorded previously in human atrium. Aims: To determine the magnitude of human atrial Ip and to investigate its sensitivity to membrane potential and extracellular K^+ concentration, $[K^+]_o$. Methods: The whole cell patch clamp technique was used in single myocytes isolated enzymatically from the right atrial appendage of 5 patients undergoing coronary artery bypass surgery. All patients were in sinus rhythm. Results: With an intracellular (pipette) Na^+ concentration of 30 mM, in the presence of time-dependent ion current blockers (Ba2+, Ni2+ and Cs+), an increase in $[K^+]_o$ from 0 to 5.4 mM produced a marked and constant outward shift in the holding current density measured at -40 mV, from -0.03±0.06 to 0.81±0.09 pA/pF ($P<0.05$, n=14 cells). This current shift was fully reversed upon returning $[K^+]_o$ to 0 mM. The Ip blocker ouabain (10 micromol/L) had no effect on the holding current measured in the presence of 0 mM $[K^+]_o$, but abolished the current produced by 5.4 mM $[K^+]_o$ (n=4). Moreover, the magnitude of the K^+- and ouabain-sensitive currents was similar, at 0.84±0.06 and 0.94±0.10 pA/pF, respectively, indicating that the current generated by increasing $[K^+]_o$ was Ip. The steady-state current voltage relationship of Ip was measured between -120 and +60 mV, using voltage step pulses (300 ms duration, 0.1 Hz, n=5) or ramps (increasing at 36 mV/s, n=8). Ip was calculated by subtracting currents recorded in the presence of 0 mM $[K^+]_o$ from those recorded with 5.4 mM $[K^+]_o$. Ip was voltage-dependent, displaying a reduced current density at hyperpolarised potentials (eg: 0.39±0.11 pA/pF at -120 mV, compared with 1.91±0.28 pA/pF at +60 mV; $P<0.05$, n=8). Ip also displayed a marked sensitivity to $[K^+]_o$, as measured by the current shift at -40 mV in response to stepwise increments in $[K^+]_o$ between 0 and 10 mM, relative to the current recorded at 0 mM $[K^+]_o$. With $[K^+]_o$ at 1 and 10 mM, the Ip density was 0.41±0.06 and 0.86±0.09 pA/pF, respectively. The $[K^+]_o$ concentration-response curve yielded an EC50 of 1.4±0.3 mM (n=5). Conclusion: We report, for the first time to our knowledge, the presence of Na^+-K^+ pump current in human atrial cells. The observed increase in Ip density both at depolarised membrane potentials and elevated extracellular K^+ concentrations indicates a potential role for this current during atrial tachyarrhythmias.

P2135 Changes in conductance and connexin43 expression in myocytes from the canine infarct border zone

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Remodelling of gap junctions in the epicardial border zone (EBZ) of healing infarct is an important factor for arrythmogenesis. In this study, we investigated the voltage-dependence and kinetics of gap junctional channels (GJC) and changes in connexin43 (Cx43) expression in EBZ cells using double patch clamp and immunoconfocal techniques. Gap junctional conductance (Gj) in cell pairs from EBZ was reduced to 30±12 nS (mean±SE, n=24) at a transjunctional voltage (Vj) of +10 mV vs. 99±13 nS (n=36, P<0.005) in controls. Steady-state conductance-voltage relationships in both EBZ and control cell pairs could be described by a two-way Boltzmann function, but Vo (transjunctional voltage halfway between maximal and minimal Gj) in EBZ cells (n=11) was shifted to +85 and -82 mV from +64and -64 mV in controls (n=9). The decay phase of gap junctional currents at Vj beyond ±50 mV could be fitted with a double exponential function. Time constants of fast and slow components at a Vj of +80 mV were 969±223 ms and 3764±1124 ms (n=11) in EBZ cells, and 344±81 ms and 1723±368 ms (n=9, P<0.05) in controls. To determine the level of Cx43 expression, we labelled randomly selected cells for immunoconfocal quantification of Cx43 and cell volume from serial optical slices. EBZ cells displayed a near significant reduction in Cx43 expression (2509 ±1213μm^3 vs 3811 ±1379μm^3: p<0.06). Cell volume from infarct hearts was reduced compared to normal (21308 ± 5567μm^3 n=10 normal vs. 28225 ± 4208μm^3, n=8 EBZ: p< 0.001). However there was no change in Cx43 immunolabelling per unit cell volume. These results suggest that changes in voltage-dependence and kinetics of Gj in EBZ cells are due to modifications of Gap junctional function and are independent of Cx43 expression.

P2136 Role of IKr for electrophysiologic heterogeneity

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Experimental findings in isolated myocytes demonstrated regional differences in the contribution of the delayed rectifier current and its slow and rapid activating components IKs and IKr. It is unknown whether these regional differences play also a role in the intact heart. We therefore investigated regional effects of the IKr blocker erythromycin in isolated intact rabbit-hearts. Methods and Results: In 13 Langendorff-perfused rabbit hearts, 300μM erythromycin led to a significant increase in QT-interval and MAP-duration at eight simultaneous monophasic action potential (MAP) recordings around the heart from the base to apex (MAP90 increase: right-epicardial 18%, left-endocardial 18%, left-epicardial 10%, p<0.05). This significantly increased dispersion of repolarization estimated as the maximal difference of the MAP recordings. Under baseline conditions (cycle lengths 900 - 300 msec) longer mean MAP90 on the right epicardium than on the left side was observed (p<0.05). There was no difference between apical and basal MAP-recordings (p=ns). After infusion of erythromycin there were still no differences between the apex and the base of the heart, but an increase of interventricular dispersion of repolarization of 42%.

Conclusion: IKr-block leads to local differences in prolongation of action potential duration in the isolated rabbit heart, (right-epicardial>left-endocardial>left-epicardial) but to no differences between basal and apical regions. This indicates a difference in the contribution of IKr between the right and left ventricle and may contribute to the electrophysiologic effects and side effects of repolarization prolonging drugs.

P2137 Regional differences in trans-sarcolemmal Ca^{2+} extrusion in left ventricular myocytes

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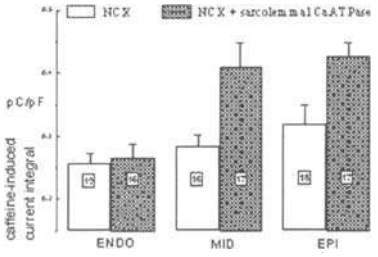
Introduction: Relaxation is dependent on Ca^{2+} removal from the cytosol via sequestration into the sarcoplasmic reticulum (SR) and trans-sarcolemmal extrusion. This study investigates the regional contribution of both the Na-Ca exchanger (NCX) and sarcolemmal CaATPase to Ca^{2+} extrusion.

Methods: Sarcoplasmic reticulum Ca^{2+} content was assessed by rapid application of caffeine in single myocytes isolated from basal sub-endocardial (ENDO), mid-myocardial (MID) and sub-epicardial (EPI) regions of the guinea-pig left ventricle. The caffeine-induced inward current reflects electrogenic NCX activity. Sarcolemmal CaATPase activity was revealed by use of the specific blocker carboxyeosin (CXE, 20μM). The difference in the integral of the caffeine-induced current (pC/pF) in the presence and absence of CXE reflects the amount of Ca^{2+} extruded via the sarcolemmal CaATPase. Data is presented as mean±SEM.

Results: The effect of CXE on the caffeine-induced current was different in the three regions studied (p<0.05, see fig). After inhibition of the sarcolemmal CaATPase, the caffeine-induced current integral was significantly increased in EPI (by 34%) and MID (by 44%) myocytes but was unaltered in ENDO myocytes.



Regional Ca extrusion mechanisms.

Conclusions: These data show a significant regional difference in sarcolemmal CaATPase activity, being greater in MID and EPI than in ENDO myocytes. In ENDO myocytes cytosolic Ca^{2+} extrusion, via trans-sarcolemmal routes, is due almost solely to NCX. However, in MID and EPI myocytes the sarcolemmal CaATPase appears to act synergistically with the NCX, promoting more efficient relaxation in these regions.

NON-INVASIVE RISK STRATIFICATION

P2138 24-hour electrocardiogram analysis in the CHRISTMAS study

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Introduction: The CHRISTMAS Study was designed to determine whether the presence of hibernating myocardium predicts the degree of improvement in left ventricular (LV) ejection fraction with carvedilol in patients with LV dysfunction and heart failure due to ischaemic heart disease.

Aim: The aim of the present study was to determine whether a treatment effect could be detected in 24-hour ECG measurements made before and after therapy by comparing patients on Carvedilol with a control group on placebo.

Methods: 24-hour ECGs were recorded, using Spacelabs Burdick recorders, at baseline and 6 months later at the end of the study. All recordings were analysed centrally in the Core ECG Lab in Glasgow using a Spacelabs Burdick analyser.

Results: Data were available from 209 patients, 100 of whom were on carvedilol. There were 183 males (mean age 61.6(8.5) years) and 26 females (mean age 67.0(10) years). Significant differences between groups were noted at the study end (see table for mean values of ECG data). With Carvedilol, RMSSD increased, SDANN decreased, and total power at max (TPMAX) and min (TPMIN) LF/HF increased, while minimum, maximum and mean heart rate over 24 hours were all significantly reduced. No differences in SDNN or triangular index (TRIDX)were detected. However, there was a significant reduction in ventricular ectopic beats and in the number of episodes of non sustained ventricular tachycardia (NSVT) in the carvedilol group. There was no evidence that these results differed according to the presence or absence of hibernating myocardium.

	RMSDD	SDANN	SDNN	TRIDX	TPMAX	TPMIN	No. VES	NSVT
T B	34.34	106.27	117.56	23.97	1962	2258	1654	1.45
T F	41.55	100.41	118.32	25.34	3478	2897	895	0.13
P B	34.93	102.17	113.61	22.29	2270	3353	1519	1.18
P F	36.04	103.25	115.26	23.22	2479	1282	1764	1.26
p value	0.020	0.036	0.322	0.665	0.030	0.027	0.012	0.003

Baseline (B) and final (F) mean values of ECG measurements in the treated (T) and placebo (P) groups.

Conclusion: These results indicate that in patients with LV dysfunction of ischaemic aetiology, carvedilol exerts significant vagal effects and markedly reduces ventricular arrhythmias regardless of the presence or absence of hibernating myocardium.

P2139 Gender differences of depolarisation and repolarisation heterogeneity

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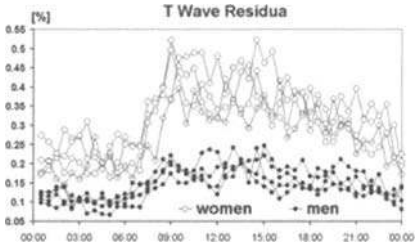
Background: The risk of torsade de pointes (TdP) is higher in women, but the mechanism of this gender difference is not known. The non-dipolar ECG components (ECG residua) are considered to directly reflect local electrical events (i.e. electrical heterogeneity). We compared QRS residua (QRS-R) and T wave residua (T-R) of standard 12-lead ECGs and their circadian variation in healthy men and women.
Methods: 24-hour 12-lead digital ECGs (SEER MC, GE Marquette, one 10-second ECG/30 sec, 2880 ECGs/24 hours) were recorded 4 times (at baseline, after 1 day, 1 week, and 1 month) in 22 healthy men (age 27±7 years) and 24 healthy women (27±8 years). Using singular value decomposition, the 12-lead ECGs were reconstructed in an optimised 8-dimensional space, in which leads 1 to 3 represented the dipolar components (i.e. the heart vector), while leads 4 to 8 represented the non-dipolar components. QRS-R and T-R were expressed as proportion (%) of the whole ECG signal (i.e. dipolar + non-dipolar components).
Results: In all 4 recordings, T-R were significantly greater in women (0.31±0.01 vs 0.15±0.005%, p<0.0000001), while QRS-R were significantly greater in men (0.46±0.003 vs 0.32±0.002%, p<0.0000001). In women, T-R exhibited significant circadian pattern with midday peak, when the gender differences were further increased (Figure). No circadian pattern of QRS-R was detected in women or men.



Conclusions: Repolarisation heterogeneity is greater in women, while depolarisation heterogeneity is greater in men. Repolarisation heterogeneity and its gender difference exhibit circadian pattern. These findings might be linked to the gender difference in the risk of TdP and to the circadian variation in the frequency of arrhythmic events.

P2140 Linkage between mechanical alternans and ST-T electrical alternans in patients with chronic heart failure

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Background and Purpose: Both progressive heart failure and sudden death due to ventricular fibrillation are major causes of death in patients with chronic heart failure. Mechanical alternans has been observed in patients with severe congestive heart failure, and it is a predictor of short life-expectancy. T wave alternans is a precursor of ventricular fibrillation in patients with acute coronary syndrome and long QT syndrome. To clarify the linkage between mechanical and electrical alternans, we investigated the occurrence of both alternans in 94 patients with chronic heart failure.
Methods: Study population contained 71 males, their mean age was 50.8±13.8. Mean LVEDVI was 127±42 and mean LVEF was 35±10%. Sixty-eight patients had sinus rhythm and remainder had atrial fibrillation. Mechanical alternans was defined when constant alternating pressure over 4 mmHg continued over 20 beats. ST-T electrical alternans was judged on standard surface ECG. Occurrence of alternans was examined at rest, during pacing tachycardia, and under stepwise dobutamine loading (2 - 4 - 8 microgram/kg/min).
Results: Prevalence of mechanical and electrical alternans were 19.1% and 4.4% at rest, 45.5% and 8.0% during pacing tachycardia, and 62.1% and 9.5% under dobutamine loading. Overall, 70 patients (74.5%) showed mechanical alternans and 10 patients (10.6%) showed T wave alternans under any condition. T wave alternans has always appeared with large mechanical alternans (mean alternating pressure 18.4±9.8 mmHg). There was no case who revealed T wave alternans without mechanical alternans. Patients with mechanical alternans revealed larger left ventricular endsystolic volume than those without, and lower left ventricular ejection fraction. Among patients with mechanical alternans, patients with electrical alternans showed lower EF than those without (27.5±4.4 and 35.1±10.2, p<0.002). Alternating pressure during electrical alternans was larger than that of mechanical alternans not accompanied by electrical alternans (18.4±9.6 mmHg vs 10.4±5.5 mmHg, p<0.05).
Conclusion: Frequency of T wave alternans was unexpectedly high in patients with chronic heart failure, especially under tachycardia or catecholamine exposure. Mechanical alternans is related to failing myocardium and ST-T electrical alternans may also be related to severer one. T wave alternans may depend on mechanical alternans.

P2141 Incidence, clinical determinants, and predictive value of microvolt T-wave alternans after acute myocardial infarction

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Background: Microvolt-level T-wave alternans (TWA) is associated with vulnerability to ventricular tachyarrhythmias. Its predictive value in pts following acute myocardial infarction (AMI) treated according to contemporary therapeutic guidelines, including a high incidence of β blocker administration, is not known.
Methods: In the present study, the incidence, clinical determinants and the predictive value of TWA (spectral method; CH2000, Cambridge Heart, Bedford, MA) were assessed in 197 consecutive AMI pts.
Results: Of 197 pts (58±11 years, 78% male; 51% anterior MI) 43 (21%) had a positive TWA. TWA was negative in 50% and incomplete/indetermined in 29% of pts. In pts with reduced LV function (EF<35%; N=50) the incidence of a positive TWA was twice as high as in those with EF>35% (34% vs 17%; p=0.02). Univariate comparison revealed no association of TWA results with other ECG-based noninvasive risk markers such as heart rate variability, baroreflex sensitivity, or QRS duration. On multivariate analysis only LVEF was an independent predictor of a positive TWA (X2=5.328; p=0.021). With respect to cardiac mortality and arrhythmic events during follow-up in this non-selected AMI population, TWA was only of borderline predictive value (RR 1.54, 95%C.I.: 0.57-4.14;p=ns).
Conclusion: The incidence of a positive TWA early following AMI is 21%. Pts with reduced LVEF have a higher probability of having a pathologic TWA result. However, the predictive value of TWA in unselected post AMI pts seems to be low.

P2142 Correlation between T-wave alternans and endomyocardial biopsy findings in patients with dilated cardiomyopathy

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Background: Patients with dilative cardiomyopathy (DCM) frequently suffer from malignant ventricular arrhythmias. T wave alternans (TWA) testing has been proposed for risk stratification but the incidence of positive test results seems markedly increased as compared to patients with coronary artery disease. The genesis of this increased TWA positivity is as yet unknown.
Objective: To compare TWA results with endomyocardial biopsy (EMB) findings in a typical population of DCM patients.
Methods: TWA was assessed in 103 DCM patients utilizing the Cambridge Heart exercise method. Positive TWA was defined as a TWA amplitude > 1.9 mV for > 1 min in > 1 ECG lead. Tracings were graded "indeterminate" if noise or premature ventricular beats prevented definite classification into positive or negative TWA or the heart rate threshold was not reached. EMB were analyzed with standardized histological (fibrosis) and immunehistological (CD2/CD3+ T-lymphocyte infiltration, expression of cell adhesion molecules/CAMs) techniques. Angiographic left ventricular ejection fraction (LVEF) averaged 38 ± 16%.
Results: In 51/103 patients (50%), TWA was graded positive, in 41/103 patients (40%) TWA was found negative, while the remaining tests were indeterminate. In 22/103 patients (21%) significantly increased CD2/CD3+ T-lymphocytes were found in the EMB specimen while 64/103 (62%) exhibited CAM abundance (CAMs), 68/103 patients (66%) showed interstitial fibrosis. TWA positivity was siginificantly associated with LVEF (47 ± 13% if TWA positive, vs. 27 ± 9% if TWA negative, vs. 42 ± 12% if TWA indeterminate, p < 0.004). In contrast, the TWA finding did not correlate with histological (interstitial fibrosis yes/no: 35/68=51% vs. 16/35=46% positive TWA results, p=ns) or immunohistological (CD2/CD3+ infiltrates yes/no: 12/22=55% vs. 39/81=48% positive TWA results, p=ns; CAMs yes/no: 28/64=44% vs. 23/39=59% positive TWA results, p=ns).
Conclusions: TWA testing yields a positive finding in 50% of DCM patients. The TWA result is unrelated to EMB findings but particularly depends on LVEF.

P2143 Value of ventricular repolarisation dynamicity for predicting implantable cardioverter therapy

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Abnormal QT dynamicity may be associated with increased risk of ventricular arrhythmias. Our aim was to investigate whether QT dynamicity measured by Holter monitoring could predict implantable cardioverter (ICD) therapy.

Methods: Patients requiring an ICD had a 24-hour Holter done systematically after implantation at hospital discharge, and were followed-up prospectively. QT dynamicity was evaluated by the linear regression slope of QT intervals plotted against RR intervals (QT/RR), using a dedicated Holter algorithm. Heart rate variability (HRV) was calculated by 24-hour SDNN.

Results: 75 patients were included (age 58±15 years,69 men.84% of patients were on beta-blockers. Appropriate ICD therapy occurred in 45 patients (60%) over a mean follow-up of 38±13 months.Results of univariate analysis are in the table. Multivariate analysis also identified slope of diurnal QT/RR as an independant predictor of ICD therapy.

Table

	ICD therapy (m±SD)	No ICD therapy (m±SD)	p
Slope QT/RR day	0.22±0.06	0.18±0.06	0.004
Slope QT/RR morning	0.20±0.07	0.18±0.067	0.20
Slope QT/RR night	0.19±0.063	0.17±0.065	0.29
Slope QT/RR 24 Hour	0.21±0.073	0.19±0.08	0.09
SDNN 24 Hours	115±42	122±51	0.83
HR day (b/min)	100±11	95±13	0.75
HR night (b/min)	92±10	89±16	0.62
LVEF (%)	35±15	45±18	0.002
VF as presenting arrhythmia (%)	37	64	0.003

Results of univariate analysis

Conclusions: Increased diurnal QT/RR interval dynamicity is independently predictive of ventricular arrhythmias in patients with an ICD. HRV appears to be devoid of any value in our study, probably because most of the patients were on beta-blockers.

P2144 Improved diagnostic ability of high-resolutin electrocardiogram by combined assessment of QRS- and ST-T-microvariability and static time-domain parameters

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Increased QRS- and ST-T micro-variability and ventricular late potentials are associated with an increased risk for malignant arrhythmias. However, the diagnostic power of the singular parameters is limited. In this study we investigated the diagnostic ability of a linear combination of both variant and static high-resolution ECG parameters.

Continuous and signal-averaged ECGs (16 bit, 2000Hz) were recorded from 51 healthy volunteers (age 24±4.2 ys) without any structural heart disease and no cardiac risk factors as well as from 44 patients (age 61±8.8 ys) with coronary heart disease, a history of myocardial infarction and inducible sustained ventricular tachycardia. Beat-to-beat micro-variability measurements of the QRS complex and the ST-T segment were based on 250 consecutive sinus beats per individual. QRS and ST-T micro-variation (QVI, TVI) was measured from the vector of standard deviations of the amplitude of corresponding points inside the normalized, spline-filtered signal. Signal-averaged ECGs were analyzed with the Simson method (QRSD, RMS, LAS). The diagnostic utility of the 5 singular parameters and all combinations of variables were evaluated by linear discriminant analysis maximizing the area under the receiver operator characteristic curve (AROC).

The singular parameters had the following values for AROC: QRSD: 0.868 (95% CI:[0.785; 0.925]), RMS: 0.736 [0.629; 0.823], LAS: 0.807 [0.710; 0.880], QVI: 0.758 [0.654; 0.841] and TVI: 0.759 [0.655; 0.843]. Among these QRSD was the most discriminative single variable. Combining QRS- and ST-T microvariability resulted in an area of 0.852 [0.758; 0.911]. The combination of QRS duration with either QRS- or ST-T variability proved to be almost equal (QRSD and TVI: 0.9 [0.822; 0.946], QRSD and QVI: 0.902 [0.825;0.947]). The combination of QRSD, QVI and TVI yielded the highest area of 0.929 [0.859; 0.963]. This parameter set had 89.5% accuracy, 86.4% sensitivity and 92.2% specificity in terms of VT patient detection.

We conclude that the combination of de- and repolarization variability with the static QRS duration markedly improves the detection of patients with inducible VT. The use of linear discriminant analysis together with ROC curves provides a powerful tool to evaluate the diagnostic ability of multivariate data sets.

P2145 VLF spectral band is superior in predicting mortality after myocardial infarction

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Heart rate variability (HRV) is a well-known univariate risk factor of mortality after myocardial infarction. Recently the value of the standard deviation of all 24 h RR intervals (SDNN) has been disputed due to the high correlation of SDNN with the mean RR interval. The aim was to investigate whether frequency domain parameters of HRV had prognostic value in the era of ace-inhibition, betablockade and statins independent of ejection fraction and the pulse (meanRR).

Methods: We examined 101 patients with 24h holter monitoring and echocardiography (Ejection fraction=30 * Wall Motion Index (WMI)). The Holter recording was performed 1-6 days after MI using the Del Mar 563 Holter System. HRV was expressed as SDNN and in the frequency domain as ULF (0-0.0033 hz), VLF (0.0033-0.04 Hz), LF (0.04-0.15 Hz) and HF (0.15-0.4 Hz).

Results: During one-year follow-up 14 deaths occurred. The table shows the performance of the investigated parameters in a univariate Cox model. In the multivariate Cox model VLF was the best heart rate variability parameter and only WMI could add independent prognostic information.

	mean ± SE	p-value<
ln VLF (au)	18.09 ± 0.08	0.00002
Wall Motion Index	1.48 ± 0.04	0.0004
ln LF (au)	17.0 ± 0.09	0.001
AGE (y)	66.7 ± 1.3	0.006
meanRR (msec)	848 ± 14	0.009
SDNN (msec)	85 ± 2	0.009
ln ULF (au)	19.40 ± 0.06	0.02
ln HF (au)	16.38 ± 0.10	0.56 (NS)

Univariate Cox analysis.

Conclusion: The frequency domain parameter VLF is the best HRV parameter and contains prognostic information independent of ejection fraction and meanRR.

P2146 Onset of ventricular tachyarrhythmias is preceded by changes in heart rate variability

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The aim of the work was to analyze if the onset of VTA is preceded by changes of heart rate variability (HRV) parameters in patients with ICD.

Methods: Time and frequency-domain analyses of HRV were performed in 54 sinus rhythm tachograms (mean duration 2 hours) recorded before onset of VTA retrieved from patients with ICD (Phylax XM, Mycrophylax Biotronik).

Results: Sudden decline in all HRV spectral components was observed 1-hour prior to VTA onset followed by gradual increase in high frequency (HF) and low frequency (LF) power for 30 minutes before the arrhythmia (HF: 13±18 vs. 29±36 ms^2 $p<0.0001$, LF: 24±32 vs. 54±66 ms^2, $p<0.0001$). Very low frequency (VLF) and total power remained at low values till VTA onset (VLF: 766 vs. 273 ms^2, $p<0.0001$). There was significant decrease in SDNN for analyzed period of sinus rhythm (70±30 ms vs. 43±31 ms, $p<0.0001$) and tendency towards shorter cycle lengths at VTA onset (809±104 vs. 767±182 ms).

Conclusions: Onsets of ventricular arrhythmias are preceded by significant changes in heart rate variability parameters already 1-hour before the arrhythmia.

P2147 HRV adjustment for age and mean RR interval disclose a different prognostic value of HRV measure in men and women with coronary heart disease

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Aim of the study.
An HRV dependence on age and mean RR interval (RRI) has been passed over in most studies that use the HRV analysis in risk stratification after MI and in heart failure. In this study we analyses whether HRV adjustment for age and RRI influences their prognostic value in the entire population and in men and women separately.
Methods: 382 patients (91f,291m, mean age 60±11 and 57±10, resp.), most of them with a healed MI (>3months) were enrolled into this study. 245 patients has undisturbed sinus rhythm, 68 had a frequent ventricular arrhythmia and 69 patients had atrial fibrillation. In each subjects a 24-hour ECG was recorded. HRV was analysed to obtain a commonly used measure (SDNN, ms) as well as an original index, HRV Fraction (HRVF,%) developed by the authors. The index has been previously shown to be applicable irrespective of cardiac rhythm disorders. Consequently, on basis of HRV analysis in a group of 302 apparently healthy subjects, a lower normal limit (LNL) for the adjusted SDNN and HRVF has been established according to the equations: SDNN = 82- 1.41age + 0.163RRI [±30%] and HRVF= 26.5 - 0.18age + 0.04RRI [±20%]. Different cut-points for both measures were applied: 1/arbitrary chosen (SDNN<70, HRVF<35%) and 2/below LNL after age- and RRI adjustment (aSDNN, aHRVF). The mean follow-up period was
19 ± 6 months. Total mortality was the end-point of this study.
Results: During the follow-up there were 50 deaths for any reason (13.1%). The mortality rate was lower in women (7/91, 7.7%) than in men (43/291, 14.8%). If arbitrary cut-points were considered, the reduced HRV was related to total mortality irrespective of gender. The log-rank values for men and women were 4.33 ($p<0.001$) and 2.88 ($p<0.01$) for SDNN<70ms, and 5.97 and 4.26 (both $p<0.001$) for HRVF<35%, respectively. When adjusted indices were used, the association of HRV and total mortality was held in men (log-rank 2.52($p<0.01$) for aSDNN, and 4.93($p<0.001$) for aHRVF. In women, however, the relation disappeared (log-rank 1.40 for both aSDNN and aHRVF).
Conclusions: The prognostic value of HRV analsis strongly depends on the chosen cut-points. If age and mean RR interval are taken into consideration, the prognostic value referes to men, while disappears in women. This suggest the necessity for re-evaluation of HRV indices' cut-points according to gender in future studies.

P2148 Different patterns of sinus pacemaker response to atrial and ventricular premature stimuli: mechanism of heart rate turbulence is still unclear

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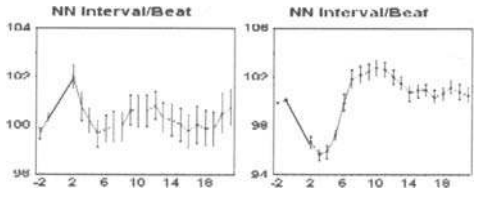
Background: Heart rate turbulence (HRT) represents a response of the sinus pacemaker to a ventricular (VPB) which consists of early acceleration phase (turbulence onset, TO) and late deceleration phase (turbulence slope (TS).
Objectives: To investigate whether phasic chronotropic response of sinus pacemaker to an APB is different from that to a VPB.
Methods: Thirty-seven pts (54±16 years, 32 men) referred for electrophysiologic evaluation for ventricular tachycardia (VT; 21 ischemic heart disease, 7 idiopathic, 9 other) underwent a stimulation protocol with single atrial and ventricular extrastimuli delivered with coupling intervals from 750 to 400 ms at a 50-ms step allowing a period of 20-sec of sinus rhythm between the stimuli. Atrial and ventricular TO and TS were calculated separately in pts with idiopathic VT and pts with ischemic cardiomyopathy and EF <0.40.
Results: In contrast to post-ventricular bi-phasic response of sinus rhythm (figure, right), a single APB caused initial brief deceleration of sinus pacemaker, followed by acceleration and late deceleration (figure, left). Three-phasic response was observed in both idiopathic and ischemic VT pts.



Sinus pacemaker response to stimulation.

Conclusions: Although APB can produce HRT operating via the same baroreceptor mechanism, the pattern of HRT post-APB is different from that post VPB, suggesting alternative mechanisma for "atrial" HRT.

P2149 QT dynamics: a new predictor of sudden death in CHF patients

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Background: QT dynamics are modified in patients with chronic heart failure (CHF) related to sympathovagal modifications. The autonomic nervous system can be investigated using heart rate variability (HRV) which is a marker of poor prognosis and mortality. The aim of this study is to examine the prognostic value of QT dynamics in total mortality and sudden death.
Methods: We prospectively included 170 CHF patients in sinus rhythm, with mean age of 56 years, and mean left ventricular ejection fraction of 28%. HRV time and frequency domains measured were obtained using 24 h. Holter ECG recordings. QT dynamics with QT/RR slope performed at the apex (QTa) and at the end of T wave (QTe) was obtained for 24 h.
Results: During the follow-up, 48 patients died, 21 patients died for sudden death. The 3 year mortality rate for sudden death was 14.1%. Qt dynamics were found to be a prognostic factor of sudden death using multivariate analysis with: QTe slope on 24 h. (cut off inf 0.28, Chi2=7.617, p=0.0058). Others Independent predictors for sudden death were: age (p=0.0205), no digoxine (p=0.0072), cardiothoracic ratio (p=0.0097) and creatinin (p=0.0003). Independent predictors for all-cause mortality in multivariate analysis were: Age (p=0.0007), Na (p=0.011) and SDNN (p=0.0004).
Conclusion: As described previously regarding ECG Holter parameter, SDNN was the best predictor of total mortality. QT dynamics demonstrate independent prognostic value of sudden death in CHF patients. These results were in accordance: SDNN reflects the global pattern of autonomic nervous system whereas QT dynamics reflects cardiac cell behavior implicated in sudden death.

P2150 The relationship between T-wave alternans and myocardial adrenergic nervous dysfunction in patients with dilated cardiomyopathy

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TWA is known as a predictor of lethal arrhythmia, myocardial adrenergic denervation is one of mechanisms that cause heterogeneity in a refractory period of ventricular myocardium and that result in the occurrence of lethal arrhythmia.
Objectives: The aim of this study is to confirm the relationship between the findings of T-wave alternans (TWA) and myocardial adrenergic nervous dysfunction using iodine-123 metaiodobenzylguanidine (MIBG) in patients with dilated cardiomyopathy.
Methods: TWA test and MIBG imaging were performed in 39 patients with dilated cardiomyopathy. We measured the alternans voltage of the vector magnitude (Valt) in the TWA test. We calculated the ratios of the heart to mediastinal activity in early images (e-H/M) and delayed images (d-H/M), and the washout rate (WR) using MIBG scintigraphy. Left ventricular ejection fraction (EF) with echocardiography and plasma norepinephrine level (NE) were also measured. Simple regression analysis was performed to evaluate the relationship between Valt and e-H/M, d-H/M, WR or EF, the analysis was also done between WR and NE.
Results: Thirty-two patients showed positive TWA and 7 patients did negative TWA. Significant negative correlations were shown between Valt and e-H/M or d-H/M (e-H/M: R=-0.40, $p<0.05$, Y=-5.0X+13.8; d-H/M: R=-0.55, $p<0.0005$, Y=-5.5X+14.7). There was significant positive correlation between Valt and WR (R=0.36, $p<0.05$, Y=0.06X+2.7), but there was no significant correlation between Valt and EF (R=0.29, p=0.07).
WR showed a significant positive correlation with NE (R=0.74, $p<0.001$). Since NE is considered to reflect the activity of the adrenergic nervous system, it was considered that WR also reflects the activity of the adrenergic nervous system.
Conclusions: These findings suggested that TWA was more closely affected by both myocardial adrenergic denervation and activation of adrenergic nervous system than by systolic dysfunction in patients with dilated cardiomyopathy.[3]

P2151 Temporal changes and prognostic significance of traditional and fractal measures of heart rate variability after acute myocardial infarction

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Background: Recent studies have suggested that fractal measures of heart rate variability(HRV) provide more powerful information than traditional time and frequency domain measures of HRV among selected patient groups with impaired left ventricular function. This study assessed the temporal changes and prognostic power of fractal and traditional measures of HRV after an acute myocardial infarction(AMI).
Patients and methods: Traditional time and frequency domain measures along with the newer fractal measures of HRV from 24-hour R-R interval recordings were measured at the baseline(n=414) and at one year after the AMI in a consecutive series of patients. The end-point of the study was cardiac death.
Results: All time and frequency domain measures of HRV increased during the one-year time course after AMI ($p<0.001$ for all, e.g. SDNN from 98±31 to 130±41 msec, $p<0.001$), but the fractal measures, such as a short-term scaling exponent alfa1(1.03±0.30 vs.1.04±0.26, NS) and power law slope beeta(-1.29±0.18 vs. -1.26±0.75, NS) did not change. When measured at one year after AMI reduced alfa1(<0.65) and beeta(<-1,55) were the only HRV indexes that predicted subsequent cardiac death; hazards ratio 4.83(95% CI 1.36-17.14, $p<0.05$) for alfa1 and hazards ratio 6.80(95% CI 1.97-23.51, $p<0.01$) for beeta.
Conclusion: In contrast to traditional HRV indices, fractal measures of HRV remain stable during the time course after AMI. Altered fractal heart rate behaviour is also a more powerful predictor of subsequent cardiac death when measured at one year from AMI.

P2152 internet-based continuous holter monitoring for the prevention of sudden cardiac death

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We have developed a pocket 12 lead ECG equipment communicating with a mobile phone and transmit the recordings via GPRS to a virtual cardiology center. The aim of the main study was to change immediately the patient management with the use of telemedicine interaction in the case of disease worsening. In the first pre-study the we assessed the prognostic value of some heart rate variability (HRV) indexes in a case control study of 32 CHF patients with cardiac death and 32 matched CHF controls. All subjects had a 48-hour Holter recordings at baseline and the 2D Poincare plot indexes were determined. All of the three typical patterns (comet-, torpedo- and fan-shaped) were quantificated: the length (P-L), the area (P-A) and the highest variability extension (P-HVE). Univariate statistical analysis (Wald-chi) showed a significant association with the outcome (p-value of P-L: 0,02, P-A: 0,01, -HVE: 0,01).In the second pre-study a wavelet analysis was performed on the Holter recordings of the same population. For each 48 hour Holter recordings twelve high resolution ECG (HR-ECG) have been computed, corresponding to twelve time sequences equally spaced over the 48 hour period. The orthogonal wavelet transform (Meyer transform) have been applied on 512 points, extending from 128 ms before the beginning of the QRS complex up to 384 ms after ORS onset The decomposition was performed for 9 different scales and four different leads. We observed a significant differences in different time-frequency locations: during the QRS, at the end of QRS and in the ST segments: p-value for 8-32 Hz is 0.01, for 62-125 Hz 0.001. In the main study 28 CHF patients were monitored with a 48 hour Holter weekly for a 6 months period. The worsening parameters of the two models (shifting patient to the sudden cardiac group) indicate immediate change of management (admission to out/inpatient cardiology department). The results show a significant decrease of primer cardiac endpoints (CHF worsening, syncope, AMI and sudden cardiac death) matched to a control 28 CHF patient population: for monitored group 3/28 for control 11/28, p-value 0.01.

P2153 Heart rate recovery immediately after exercise as a predictor of mortality after an acute myocardial infarction

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Background: Altered cardiovascular autonomic function has been shown to indicate an increased risk for death among the patients with a prior acute myocardial infarction (MI). An impaired heart rate (HR) recovery after the exercise has been recently shown to provide prognostic information among the mixed patient populations undergoing diagnostic exercise tests.
Methods: This study was designed to assess the predictive power of HR recovery in a consecutive serie of patients with an acute MI undergoing the predischarge exercise testing.
Results: Two hundred and twenty-nine post-MI patients who underwent exercise test after an acute MI were followed-up for a mean of 30±13 months. All the patients were on beta-blocking therapy at the time of exercise test. HR recovery was defined as the difference in the HR between the peak exercise and after 1 minute recovery. There were 17 deaths (7.4%) during the follow-up. An abnormal HR recovery, defined as a reduction of HR <12 bpm during the first recovery minute, predicted overall mortality with a hazards ratio of 5.0 (95% CI from 1.4 to16.7, $P< 0.02$) in univariate analysis. The most powerful predictor of all cause mortality was a combined variable of impaired weight adjusted exercise capacity and abnormal HR recovery with Hazard ratio 9.1; (95% CI from 3.2 to25.8, $p < 0.001$) in univariate analysis. Both impaired exercise capacity and abnormal HR recovery were, stronger predictors of death than conventional HR variability index standard deviation of N-N intervals measured from 24-hour ambulatory recording. After adjusting for age, functional class and ejection fraction, an impaired HR recovery remained as a significant independent predictor of death (adjusted hazards ratio 4.7 (95% CI from 1.3 to 16.6; $P<0.02$).
Conclusion: An impaired weight adjusted exercise capacity and abnormal HR recovery are powerful predictors of death among the patients surviving an acute MI. These simple measurements during the routine pre-discharge exercise test perform better in prediction of mortality than the traditional clinical or HR variability indices.

P2154 Temporal repolarization inhomogeneity after successful primary percutaneous coronary intervention for acute myocardial infarction: impact of admission troponin T

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Objectives: This study sought to determine the temporal resolution of reperfusion arrhythmias and ventricular repolarization inhomogeneity after successful primary percutaneous coronary intervention (PCI) in acute ST-segment elevation myocardial infarction (AMI) depending on admission cardiac troponin-T (cTnT) status.
Background: Presence of admission cTnT identifies a high risk subgroup in patients with AMI. As a substantial number of these patients is suffering from malignant ventricular arrhythmias, we hypothesized that there is a relation between cTnT status on admission and inhomogeneity of ventricular repolarization.
Methods: Temporal fluctuations of ventricular repolarization were studied during and after primary PCI (TIMI 2 and 3) in 94 consecutive patients with a first AMI by continuous beat-to-beat QT-interval measurement, performed from Holter monitoring initiated on admission. CTnT levels on admission were >0.1ng/ml in 53 patients (cTnT+) and <0.1ng/ml in 41 patients (cTnT-).
Results: There were no significant differences in baseline clinical characteristics between both groups. The incidence of severe reperfusion arrhythmias was significantly higher in cTnT+ patients within the first two hours after recanalization. The course of QT-interval revealed a significant decline ($p<0.001$) after recanalization of the infarct related vessel within 10 hours in both groups, however, hourly values were significantly lower and normalization of parameters of QT-interval was more rapid in cTnT- versus cTnT+ patients in this period (QTc: 438.5±28.3 vs. 449.3±35.3 ms (hour 1)($p<0.01$); 413.6±35.8 vs. 420.1±39.2ms (hour 10)($p<0.05$)). QT-interval variability also significantly declined within four hours after PCI ($p<0.001$), and likewise cTnT- patients exhibited lower values in this period (QTSD: 29.7±6.8 ms vs. 33.5±10.5 (hour 1)($p<0.01$); 23.0±6.1 vs. 25.9±7.5 ms (hour 4)($p<0.01$)). Mean RR-interval was significantly lower in cTnT+ patients (716.5±80 vs. 773.3±109 ms ($p<0.01$)), and its increase after PCI was not as marked as in cTnT- patients.
Conclusions: Positivity of cTnT on hospital admission is associated with a significantly higher temporal inhomogeneity of ventricular repolarization and a higher incidence of malignant reperfusion arrhythmias suggesting a more advanced microvascular injury. Early successful primary PCI ultimately results in a significant recovery of parameters of QT-interval and mean RR-interval in all patients although it was significantly delayed in cTnT+ patients.

P2155 Both forms of preconditioning reduce QTc value in patients with first non ST-segment elevation myocardial infarction (NSTEMI)

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Introduction: Preinfarction angina (PA) consists a strong clinical correlate to ischemic preconditioning (PC). The phenomenon of late appearance of the protective effect of PC recently is thought that may extend over a period of one to three days, unlike the protection afforded by the classic PC phenomenon. The aim of the present study is to evaluate the impact of both forms of PC on QTc value, in patients (pts) with a first NSTEMI.
Methods: 48 pts, with first NSTEMI and with angiographically proven poor or none collateral circulation (0-1 according to Rentrop classification) were enrolled in the study. All pts underwent coronary angiography in the first 72 hours from admission. Pts were divided into three groups. First group consisted of 20 pts who did not report PA (typical chest pain episodes lasting less than 20 minutes, PA-); second group consisted of 12 pts with PA within 24 hours prior to admission (24h PA+); and the third group consisted of 16 pts who reported PA within 24 to 48 hours prior to admission (48h PA+). A standard 12 lead ECG, was obtained at admission and discharge and QTc values were evaluated by two separate readers, using Bazzet's formula. The primary outcome was determined as the effect of PA on QTc value at discharge. We performed two series of analyses in regards to the outcome: group (24h PA+) pts versus (PA-) pts and group (48h PA+) pts versus (PA-) pts, reflecting the classic and the delayed form of PC respectively versus no PC effect. Statistical analysis was performed using t-test and statistical significance was defined as a p-value <0.05.
Results: There were no significant differences between the three groups concerning demographic data, infarct location, severity of coronary heart disease and therapy received. The table reviews all relevant QTc data.

	PA- (n=20)	24hPA+ (n=12)	p	PA- (n=20)	48hPA+ (n=16)	p
QTc admission (msecs)	417±59	432±19	NS	417±59	440±38	NS
QTc discharge (msecs)	455±53	412±50	0.015	455±53	417±29	0.033

The PC effect on QTc value

Conclusions: Both forms of preconditioning, similarly and significantly reduce QTc value at discharge in pts experiencing a first NSTEMI, documenting possible protection from future arrhythmic events and producing evidence for the true existence of the second window of protection of PC in humans.±

P2156 Simple cardiovascular reflex tests predict death during first 6 months after acute myocardial infarction

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Objective: To evaluate prognostic value of heart rate (HR) response to simple provocative maneuvers performed during hospitalization because of myocardial infarction (MI).
Material: 187 patients with acute MI (68,4% men) aged 34-75 (60.5±9.7) years. Methods. Valsalva maneuver (VM) with calculation of Valsalva ratio (VR) and deep breath test (DB) were performed on days 4-11 (7.8±0.9) of MI when 93.6% of patients received beta-blockers. Technique of DB test: a patient breathed 6 times per minute, from each of 6 breathing phases at first minute of test a mean of longest and shortest RR intervals was calculated and maximal and minimal HR determined, then difference of these HRs (HRD) was calculated.
Results: During period of follow up for 6.5±0.7 months there were 13 cardiovascular deaths (8 sudden). According to univariate logistic regression analysis result of VR was predictor of cardiovascular death together with such classical predictors as age, history of angina and MI, postinfarction angina, ejection fraction, and clinical heart failure (HF) on the day of test. Multivariate (step-up) analysis showed that independent predictors of cardiovascular death were history of MI, postinfarction angina, and VR (*OR* 0.001, 95% CI 0.0001-0.9). VR and ln HRD were in the list of univariate predictors of sudden death (OR 0.0001, 95% CI 0.0001-0.2 and OR 0.3, 95% CI 0.1-1.03, respectively) with age, history of MI, postinfarction angina, clinical HF on the day of test. Independent predictors of sudden death were ln HRD (OR 0.3, 95% CI 0.1-0.9) and clinical HF on the day of test.

VR and HRD in survivors and nonsurvivors

		Survivours	Nonsurvivours	p
Valsalva ratio	Cardiovascular mortality	1.2+0.2	1.1+0.07	0.02
	Sudden death	1.2+0.2	1.1+0.04	0.03
HRD	Cardiovascular mortality*	5.5 (3.6; 8.9)	3.3 (2.6; 9.6)	0.1
	Sudden death*	5.5 (3.6; 8.9)	3.2 (2.1; 9.3)	0.03

* medians (25, 75 percentiles)

Conclusion: HR response to VM and DB predict cardiovascular death during first 6 month after acute MI. While decrease of Valsalva ratio was primarily associated with cardiovascular mortality result of DB was more closely related to sudden death.

P2157 Cardiac arrhythmias and risk stratification after myocardial infarction (CARISMA): results of the pilot study

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Background: CARISMA is a multicenter, observational study enrolling patients with an acute myocardial infarction (AMI) and an ejection fraction < 40% in whom the incidence of tachy- and bradyarrhythmias is prospectively assessed by means of an insertable loop recorder (ILR) providing automatic arrhythmia detection. At 6-weeks post-MI, extensive risk-stratification tests (EP-testing, Holter, HRV, late potentials, QT dispersion, T-wave alternans) are performed to assess their predictive value for life-threatening arrhythmias.
Results: The pilot study included 28 patients with a mean follow-up of 52 days. The ILR detected atrial tachyarrhythmias in 6 patients, non-sustained ventricular tachycardia (nsVT) in 2, idioventricular rhythm in 2, and intermittent 3° AV-blocks in 3. Four patients with nsVT documented either by ILR (n=2) or Holter (n=2) were inducible into sustained VT and received an ICD, and a pacemaker was implanted in the 3 patients with intermittent 3° AV-blocks.
Conclusions: ILR disclosed significant arrhythmias in a large proportion of patients shortly after their acute MI. An indication for implantable device therapy was also detected in a relatively high number of patients enrolled in the CARISMA pilot study.

P2158 Effects of aerobic exercise training on nonlinear dynamics and variability of heart rate in elderly people

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Earlier studies have reported mixed results as to the effect of aerobic exercise training on heart rate (HR) variability and none of them reported the effects on nonlinear measures of HR dynamics. We analyzed the effects of 12-week supervised aerobic exercise training (60 minutes per session, three times a week) on HR dynamics and variability in 12 healthy elderly volunteers (age range; 64-77 years, 6 males). At baseline and the end of the exercise training, we obtained 24-hr ambulatory ECG and assessed irregularity and complexity of HR dynamics by approximate entropy (ApEn) and fractal correlation (short- and long-term fractal scaling exponents of detrended fluctuation analysis [alpha 1 and 2]), respectively, and HR variability by time- and frequency-domain measures (standard deviation of normal-to-normal R-R intervals [SDNN] and high-frequency [HF; 0.15 to 0.4 Hz], low-frequency [LF; 0.04 to 0.15 Hz], very-low-frequency [VLF; 0.0033 to 0.04 Hz] and ultra-low-frequency [ULF; <0.0033 Hz] power). After completion of the exercise training, oxygen uptake (*VO2*) at lactate threshold increased (15.9 ± 2.4 to 18.9 ± 4.2 [ml/kg/min], p = 0.026) and 24-hr mean HR decreased (73 ± 7 to 70 ± 7 [beats/min], p = 0.014). However, no significant changes were observed in either nonlinear measures of HR dynamics or any measure of HR variability (Table).

Changes in HR dynamics and variability

	Baseline	After Training	p
ApEn	1.15 (0.16)	1.19 (0.14)	p = 0.33
Alpha 1	1.17 (0.19)	1.13 (0.18)	p = 0.29
Alpha 2	1.13 (0.06)	1.13 (0.07)	p = 0.96
SDNN (ms)	146 (29)	138 (30)	p = 0.11
ln HF (ln[ms2])	5.25 (1.05)	5.62 (0.96)	p = 0.06
ln LF (ln[ms2])	6.01 (1.08)	6.20 (1.02)	p = 0.23
ln VLF (ln[ms2])	7.09 (0.59)	7.28 (0.58)	p = 0.14
ln ULF (ln[ms2])	9.60 (0.57)	9.75 (0.40)	p = 0.36

Values are means (SD). For abbreviations, see text.

Our results indicate that measures of HR dynamics and variability do not show changes coupled with an improvement of aerobic capacity or negative chronotropic effects induced by exercise training. At least in elderly people, prognostic associations reported for these measures seem unexplained by the effects of fitness level on these measures.

ATRIAL FIBRILLATION – STROKE

P2159 Relationship of plasma von willebrand factor and soluble p-selectin to echocardiographic findings in 1308 patients with atrial fibrillation

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Background: Several transthoracic echocardiographic (TTE) parameters have been shown to predict stroke in atrial fibrillation (AF), with left ventricular (LV) dysfunction the only independent predictor. AF is associated with increased levels of plasma von Willebrand factor (vWf, an index of endothelial damage/dysfunction) and soluble P-selectin (sP-sel, an index of platelet activation), but the relationship to TTE parameters is unclear.
Methods: We measured plasma vWf and sP-sel levels (ELISA) in 1308 participants (mean age 69,sd9 years; 75% male) enrolled in the Stroke Prevention in AF (SPAF) III trial and related these indices to TTE data (LV function, atrial size, valve disease).
Results: vWf levels were higher in patients with an abnormal mitral valve (151sd30 vs. 143sd31 iU/dl, p<0.001), LV fractional shortening <=25% (152sd29 vs. 145sd31 iU/dl, p=0.004) or large left atrial size (>median of 4.7 cm) (148sd30 vs. 144sd32 iU/dl, p=0.02). Compared to patients with normal LV function, vWf levels were significantly higher in patients with severe LV dysfunction (p=0.005), table 1. vWf levels were unaffected by moderate-severe mitral regurgitation (p=0.4). However, after adjusting for potentially confounding clinical factors known to affect vWf level in AF (age, prior stroke, body mass index, recent heart failure, diabetes), the relationships between TTE parameters and vWF were no longer statistically significant.

	Normal LV Function (n=988)	Mild LV Dysfunction (n=154)	Moderate LV Dysfunction (n=91)	Severe LV Dysfunction (n=76)	p
vWf (iU/dl)	145 (31)	148 (30)	152 (30)	156 (29)	0.005
sP-sel (ng/ml)	34 (13)	35 (15)	34 (12)	33 (11)	0.7

Relationship of vWf and sP-sel to Degree of Echocardiographic LV Dysfunction (values expressed as mean (sd))

sP-sel levels were higher in patients with an abnormal mitral valve (35sd14 vs. 33sd13 ng/ml, p=0.047), but statistical significance was quickly lost after adjusting for confounders and sP-sel was unrelated to other TTE findings (all p>0.5). Conclusion: TTE features which predict stroke and thromboembolism in AF were closely related to evidence of endothelial damage/dysfunction (vWf) but not platelet activation (sP-sel), although the observed relationships may be due to the presence of additional disease states.

P2160 Randomized study of aspirin versus warfarin for high-risk mitral rheumatic atrial fibrillation patients

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Background: Aspirin has been shown to be an option to warfarin to prevent embolic events in some studies in non-rheumatic atrial fibrillation patients. In order to evaluate if these data may be applied to high-risk rheumatic patients - with mitral valve disease and atrial fibrillation - we performed a randomized, prospective trial.
Methods: We assigned 229 atrial fibrillation rheumatic patients, medium age: 50±12.23 years, 78% female, with either mitral stenosis (62.2%), mitral regurgitation (8.4%) or mitral bioprosthesis with mild regurgitation (29.9%) to receive aspirin, 200 mg/day (Aspirin group -AG), or warfarin (Warfarin group-WG), with a target international normalized ratio of 2 to 3. We performed clinical, laboratory and echocardiography analysis and patients were followed for 56.64±17.64 months. 110 patients were assigned to receive aspirin and 119 to warfarin. 90% had left atrial spontaneus contrast, and 17% had left atrial thrombus in transesophageal echocardiography (TEE) There were no statistical difference between these groups regarding to age, sex, mitral valve disease, functional New York Heart Association class, diabetes, cholesterol and trygliceride serum levels, smoking, left ventricular function and diameters, left atrial diameter, mitral valve area, and presence of left atrial thrombus or left atrial spontaneus contrast on TEE.
Results: We observed 15 (13.6%) embolic events (EE) in the AG and 24 (20.2%) EE in WG (p=ns), of which, 21 had INR<2 during EE. There were 21 gastrointestinal bleeding in WG and 09 in AG (p=0.034). Minor bleeding was also more frequent in the WG (p<0.01). Multivariate analysis identified triglyceride level over 250 mmol/dl (Odds ratio=5.72, 95% C.I. 1.64 – 20.31 and low density lipoprotein cholesterol over 160 mmol/l (Odds ratio=4.08, 95% C.I. 0.87 – 19.22) as risks factors for EE in the WG and in the AG, respectively.
Conclusions: 1. Aspirin had, in this population,the same efficacy as warfarin for the prevention of embolic events. 2. Warfarin had higher risk for haemorragic events than aspirin. 3. High lipoprotein serum levels were independent risk factors for embolic events in rheumatic mitral disease atrial fibrillation patients.

P2161 Repetitive premature atrial contractions as a risk factor for paroxysmal atrial fibrillation in patients with stroke

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Background: Paroxysmal atrial fibrillation (PAF) is a frequent cause of cerebrovascular insult (CVI). Ambulatory ECG often fails to demonstrate PAF. Repetitive ectopic atrial activity can trigger PAF in patients with atrial myopathy (substrate). The aim of this study was to correlate the frequency of premature atrial contractions (PACs) with the occurrence of PAF during the prospective follow-up of patients who suffered CVI.
Method: The frequency of PACs in 24 hr ambulatory ECGs was assessed in consecutive CVI patients with (n=46) and without (n=108) PAF, as well as in age and gender matched controls (51). Patients where grouped into quartiles according to the frequency of the PACs. Patients with CVI and without PAF were studied prospectively. An echocardiography was performed to determine the presence of a substrate for PAF and the cardiovascular risk factors (cvRF) were assessed. Occurrence of clinical episodes of PAF and its correlation with the presence of repetitive triggers in ambulatory ECG was assessed.
Results: After a mean follow-up of 22.6 months PAF occurred in 12 of 99 patients with CVI and initially without PAF. In the quartile with the most frequent PACs (>120/24 h) PAF was significantly more frequent than in the three other quartiles (7/22 pts vs. 5/77 pts, respectively, p<0,0001). The patients who developed PAF in the follow-up had significantly more frequent PACs than the group without PAF (143 ± 480/24h vs. 2237 ± 3866/24h, p<0,0001). There was no significant difference between the quartiles in respect of left atrial size, left ventricular mass, ejection fraction and the number of cvRF.
Conclusion: In patients with CVI and without PAF, there is a correlation between repetitive PACs (>120/24hr) and the subsequent occurrence of PAF. Thus, repetitive PACs are a marker of an increased susceptibility to develop PAF in the follow-up. An aggressive screening for PAF should be performed in patients with CVI and repetitive PACs.

P2162 Thrombin-antithrombin levels are directly associated with heart rate at entry in patients with non-valvular atrial fibrillation

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Atrial fibrillation (AF) represents a hypercoagulable state. However, the mechanisms through which AF produces this state are still not well understood. We sought to determine which clinical and echocardiographic markers were associated with a prothrombotic state assessed by determinations of the thrombin-antithrombin complex (TAT)in patients with non-valvular AF.
We studied 88 patients (50 males, mean age = 67 ± 14 years old), 58 with paroxysmal AF and 30 with chronic AF. We studied clinical, echocardiographic and thrombin-antithrombin levels in all the patients at baseline. Fifty percent of the patients were > 70 years old, 56% were hypertensives, 16% diabetics and 35% had associated CAD and/or dilated cardiomyophaty. Five patients reported previous embolic events. TEE, performed within in the first 3 days, showed that 57% of patients had an enlarged left atrium (>45 mm), 54% had left atrial echo contrast and/or presence of thrombus, and 13% had evidence of systolic left ventricular dysfunction. Mean heart rate at entry was 118 ± 29. Mean TAT levels at baseline were significantly higher in AF patients than in a matched control group in sinus rythm (32.6 ± 66 versus 2.7 ± 3.3 ng/L, p < 0.001). There was no significant difference in TAT levels between paroxysmal and chronic AF patients (34.2 ± 58 and 204.3 ± 425.1 ng/L respectively, p = 0.19). Elevated TAT levels were not related to age, history of hypertension or diabetes, structural heart disease, left atrial enlargement, atrial echo contrast and/or thrombus. After multivariate regression analysis, the only clinical parameter significantly related to elevated TAT levels was the heart rate at entry (r = 0.31, p = 0.02), even after adjustments for the classical clinical and echocardiographic risk factors for embolism and use of antiarrhytmic drugs before admission.
Conclusions: This study is the first to demonstrate that TAT levels, a marker of activation of coagulation, are directly associated with the heart rate at entry in patients with AF, independently of traditional risk markers. Heart rate control at entry might be an important bedside marker to modify the prothrombotic state of patients with AF.

P2163 Losartan decreases the risk of stroke in hypertensive patients with atrial fibrillation and left ventricular hypertrophy

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Background: Atrial fibrillation is a common arrhythmia, and a strong risk factor for stroke. The risk for stroke is further increased in those patients with atrial fibrillation and concomitant arterial hypertension. The Losartan Intervention For Endpoint reduction in Hypertension (LIFE) Study included 9193 patients, (mean age 66.9 ± 7.0 years, 54% woman) with essential hypertension, (BP 174/ 98 mm Hg) and ECG documented left ventricular hypertrophy. Patients were randomised to double blind treatment with the angiotensin II antagonist (AIIA) losartan or the betablocker atenolol. Additional open label antihypertensive treatment to reach the target blood pressure of p < 140/90 mm Hg, except other betablockers, ACE inhibitors and AIIAs, was accepted. In a substudy patients with atrial fibrillation at baseline were included, and the effects on the risk of stroke were compared. **Results:** 324 patients, (mean age 70.5 ± 6.4 years, 42.3% female) were included, and followed for a mean of 4.8 years. 150 patients (70.0 ± 6.7 years, 41.3% female) were allocated to losartan and 174 (70.9 ± 6.1 years, 43.1% female) to atenolol. In the losartan group mean BP was 176.1/97.0 (± 13.6/9.9) mm Hg and Framingham risc score 26.9 ± 10.4, compared to 175.5/95.3 (± 13.9/10.5) mm Hg and 26.9 ± 10.4 in the atenolol group. Of the losartan allocated patients 33.3% had coronary heart disease (CHD), 12.7% cerebrovascular disease (CVD) and 21.3% diabetes mellitus (DM) compared to a prevalence of 29.3% CHD, 16.1% CVD and 27.6% DM in the atenolol group. In those patients allocated to losartan 12% (n= 18) of the patients experienced a stroke while 21.3% (n= 37) of the patients in the atenolol group had a stroke. This difference was statistically significant, p= 0.018, with an Adjusted Hazard Ratio of 0.5 (95% C.I. 0.29 - 0.89).
Conclusion: In hypertensive patients with left ventricular hypertrophy and atrial fibrillation, treatment with losartan in comparison with atenolol, significantly reduced the incidence of stroke. 11 patients treated with losartan instead of atenolol for 4.8 years will prevent one stroke.

P2164 Time required to achieve therapeutic anticoagulation with warfarin prior to cardioversion for atrial fibrillation

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Background: Anticoagulation with warfarin for three weeks and transesophageal echocardiography are two strategies used prior to cardioversion for atrial fibrillation to minimize the risk of thromboembolism. The degree of post-cardioversion atrial mechanical dysfunction and atrial electrical remodelling are directly related to the duration of atrial fibrillation.
Aim: The purpose of this study was to determine the actual time required to achieve therapeutic anticoagulation with warfarin prior to cardioversion.
Methods: Sixty-two (38 men) consecutive patients with non valvular atrial fibrillation who were started on warfarin therapy prior to an elective cardioversion procedure were identified. Patients were followed in a hospital anticoagulation service and the warfarin dose was adjusted using a predetermined nomogram to maintain an international normalized ratio (INR) of 2.0 to 3.0. Patients were scheduled to undergo cardioversion after the INR was greater than 2.0 for 3 consecutive weeks. The mean age of the patients was 66 ± 11 years, the mean duration of atrial fibrillation was 3.1 ± 2.2 months (range 0.5-6 months) and 42% pts had structural heart disease.
Results: The mean time required to achieve the first therapeutic INR was 1.8 ± 1.5 weeks (range 0.2-4.2). The mean time required to achieve 3 weeks of therapeutic anticoagulation was 5.2 ± 2.6 weeks (range 2.9-9.8 weeks). Patients underwent cardioversion 6.9 ± 2.7 weeks after initiation of warfarin (range 3.3-11.8 weeks).
Conclusion: When initiating warfarin therapy prior to cardioversion for atrial fibrillation, at least 6 weeks are required to achieve 3 weeks of therapeutic anticoagulation, even when patients are closely monitored by an anticoagulation service. Early cardioversion using a transesophageal echocardiography-guided approach would reduce the overall duration of atrial fibrillation by almost two months.

P2165 Evidence of a temporary prothrombotic state in patients in sinus rhythm after electrical cardioversion of persistent atrial fibrillation

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Introduction: It is assumed that restoration of sinus rhythm (SR) reverses the prothrombotic state associated with persistent atrial fibrillation (AF). Electrical cardioversion (DC-CV) is used to restore SR but is associated with a temporarily increased risk of thromboembolism particularly within the first 10 days. The reasons for this are unclear.
Method: We describe the sequential changes in plasma concentration of tissue factor (TF), von Willebrand factor (vWF) and thrombin-antithrombin (TAT) in patients with persistent AF undergoing DC-CV. 46 patients were studied with 25 age- & sex-matched controls in SR.
Results: Plasma concentration of TF in patients was higher at presentation than in controls {127.3 (SD 57.0) pg/ml vs 86.1 (SD 38.2) pg/ml, P=0.01}. Plasma TF was higher at 10 days than 1 hour after DC-CV {135.8 (85.4) pg/ml vs 109.5 (54.2) pg/ml, P=0.03}. There was no change from baseline to 3 months in the 12 patients who remained in SR {127.4 (68.7) pg/ml vs 113.5 (70.9) pg/ml, P=0.18}. Plasma vWF in patients was elevated compared to controls {mean 2.00 (SD 0.60) IU/ml vs mean 1.38 (SD 0.46) IU/ml, P<0.001}. There was an increase in plasma vWF from 1 hour to 10 days post DC-CV, but only in those 21 patients remaining in SR {2.23 (0.48) IU/ml vs 2.49 (0.63) IU/ml, P=0.01}. There was no change from baseline to 3 months in patients who maintained SR {2.23 (0.71) IU/ml vs 2.21 (0.55) IU/ml, P=0.92}. In patients not on warfarin at presentation (n=22), plasma concentration of TAT was not different to controls {2.79 (SD 1.16) μg/ml vs 2.89 (SD 1.16) μg/ml, P=0.77}. TAT was higher at 10 days than 1 hour after DC-CV, with those maintaining SR significantly elevated from those who had relapsed to AF {2.08 (1.54) μg/ml vs 1.31 (0.42) μg/ml, P=0.04}, there was no difference in INR between these groups.
Conclusions: 10 days after DC-CV patients in SR had higher plasma TF, vWF and TAT compared to those in AF. But in those maintaining SR for 3 months there was no change from presentation. We postulate that this temporary prothrombotic state results from the altered haemodynamics associated with atrial stunning. This observation may explain the increased risk of thromboembolism in the 10 days after DC-CV.

RESYNCHRONIZATION THERAPY IN HEART FAILURE PATIENTS: PREDICTING FACTOR OF SUCCESS

P2166 Can we predict who is going to improve after the implant of a CRT device?

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Recent clinical studies have demonstrated the ability of cardiac resynchronization therapy (CRT) to improve exercise capacity in severe heart failure (NYHA III-IV) patients with wide QRS. The goal of this study was to analyze the correlation between baseline clinical variables, including the acute response to pacing and the changes obtained in peak VO2 (DpVO2) after 3 months of CRT. Methods: We analyzed 64 patients with complete baseline values and complete pairs of pVO2 measurements before and after CRT from the PATH CHF II trial. The following clinical variables were analyzed: baseline LVEF, percent change in LV dP/dtmax with CRT (DdP/dtmax), baseline LVEDP, baseline pulse pressure (bPP), QRS width (QRSw), baseline pVO2 (bpVO2) and the difference between the maximum percentage increase in PP during acute application of CRT and the percentage increase in PP at the chronically programmed AV delay (PPmax-PPprog). A multivariate linear regression analysis between these variables and DpVO2 was used to quantify the ability of these parameters to predict changes in pVO2. Results: Changes in peak pVO2 were significantly correlated with the studied pre-implant clinical variables (p < 0.0001; r = 0.73). The resulting multivariate equation was: DpVO2 = 0.0431 * QRSw + 0.0353 * DdP/dtmax + 0.1074 * (PPmax-PPprog) - 0.3091 * bpVO2 - 0.0292 * bPP - 0.0856 * LVEDP - 0.0719 * LVEF + 2.8921. The p values for the coefficients were: 0.01, 0.08, 0.003, 0.006, 0.13, 0.01, 0.11 respectively. Conclusions: These data suggest that the change in pVO2 obtained after 3 months of CRT may be estimated from baseline clinical and hemodynamic data. The largest benefit in pVO2 was obtained by the patients who had the widest QRS with the largest acute response in dP/dtmax, the lowest PP response at the programmed AV delay, the lowest bpVO2, the lowest bPP, the lowest LVEDP and the lowest LVEF. The finding that the combination of a high optimum DdP/dtmax and a low PP percentage increase at the programmed AV delay is associated with a larger improvement in DpVO2 triggers a very important clinical question about the relative importance of optimizing preload versus optimizing resynchronization, strongly suggesting that setting the AV delay to optimize preload may not be the correct therapeutic target.

P2167 Predictive factors of long-term functional improvement after biventricular resynchronisation

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Purpose: The biventricular pacing has recently been proposed as a treatment of refractory heart failure. There is a paucity of data concerning the long term follow up after ventricular resynchronisation. This study analyse predictive factors of functional improvement after biventricular pacing.
Patients and method: From April 1997 to December 2000 successful implantation of biventricular pacemaker was performed in 29/31 (94%) of patients. The mean age was 70.2± 6.9 years, 75.9% were men, 56.2% were in NYHA class III and 43.8% in class IV. The sinus rhythm was present in 69% of patients. The patients with atrial fibrillation were treated systematically during the procedure by atrioventricular junction radio frequency. After a mean follow up of 16.1 ± 8.0 months, the NYHA class, Minnesota score, echocardiographic left ventricular ejection fraction (LVEF) and the number of hospitalisations were noticed for each patient.
Results: In the whole group, the LVEF improved from 23.6 ± 9.1% to 31.3 ± 11.4% (p=0.01), the NYHA class decreased from 3.45 ± 0.5 to 2.1 ± 0.6 (p = 0.01), and the Minnesota score decreased from 40.3 to 23.5 points (D = 42%; p < 0.01). The patients initially in NYHA class IV improved more than patients in class III (LVEF from 20.6 ± 7.4% to 32.6 ±12.2% vs. 25.9 ± 9.9% to 30.2 ± 11.0%, p = 0.03; NYHA class from 4.0 to 2.1 ± 0.7 vs. 3.0 to 2.1 ± 0.6, p = 0.02). The reduction of number of hospitalisations in the follow up, comparing to the period of 12 months preceding the procedure, were more important in the NYHA class IV (from 4.0 ± 1.2 to 0.3 ± 0.6 vs. 1.9 ± 1 to 0.4 ± 0.6; p = 0.002). The evolution of Minnesota score was comparable in the two groups.
Conclusion: During a follow up of 16 months after ventricular resynchronisation the functional improvement is more pronounced in patients initially in NYHA class IV to patients in class III.

P2168 Correlation of brain natriuretic peptide release and exercise capacity in patients with heart failure and cardiac resynchronization therapy

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Background: Brain natriuretic peptide (BNP) levels are highly expressed in pathological hemodynamic conditions and correlate with cardiac functional parameters like left ventricular (LV) ejection fraction (EF) or LV wall stress. Cardiac resynchronization therapy (CRT) improves cardiac hemodynamics and functional status in patients (pts) with heart failure (HF) and left bundle branch block (LBBB). We investigated the effects of CRT on BNP levels, cardiopulmonary exercise testing (CPX) and 6 min walk testing (WT) in these pts.
Methods: 12 pts (6f, 6m, 63±8y) with severe HF (mean EF 21±5%, NYHA II 2 pts, NYHA III 9 pts, NYHA IV 1 pts), LBBB (QRS 165±31 ms) receiving CRT for dilative (8 pts) or ischemic cardiomyopathy (4 pts) were investigated. BNP levels were determined with the Triage BNP test (Biosite Diagnostics, USA) at rest. Cardiopulmonary exercise testing (CPX) was performed on a cycle with incremental work load. Maximum oxygen consumption (VO2max) and oxygen consumption at the anaerobic threshold (VO2-AT) were measured. A 6-minute walk test (WT) was performed on a 45 m long plain floor. BNP blood samples and CPX and WT data were collected before pacemaker implantation (basal) and after 15±11 weeks of continuous CRT (VDD mode). As BNP levels depend on renal function, serum creatinine and blood urea nitrogen (BUN) levels were simultaneously measured.
Results: The effects of CRT on BNP levels, CPX, WT and renal function are shown in the table.

Effects of CRT

	BNP (pg/ml)	VO2max (ml/min/kg)	VO2-AT (ml/min/kg)	WT (m) (m)	Creatinine (mg/dl)	BUN (mg/dl)
Basal	676±405 (232-1300)	12.9±3.2	9.9±2.4	310±119	1.5±0.6	68±35
CRT	380±290* (124-956)	16.0±3.8*	13.5±2.8*	414±69*	1.6±0.7	69±38
R		-0.61#	-0.66#	-0.62#		

Mean ±SD; *p<0.05 vs basal; R = correlation vs BNP, #p<0.05

Conclusion: Chronic CRT leads to a significant decrease in BNP release and improvement of exercise capacity with an inverse correlation of functional tests (VO2max, VO2-AT, WT) to BNP release. Thus, decreasing BNP levels are an indicator of improved functional status during CRT and may therefore be used as a marker for therapeutic efficacy of CRT in patients with advanced HF and ventricular conduction disturbance.

P2169 Interventricular delay predicts clinical outcome in CHF patients undergoing resynchronization therapy

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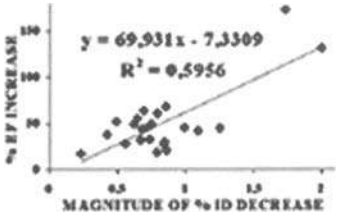
Cardiac resynchronization by biventricular pacing (BiV) has recently become a valuable tool in the treatment of end stage congestive heart failure (CHF). Unfortunately, not all the patients (pts) benefit by this therapy and no predicting factors of favorable outcome have been unequivocally reported. To identify potential predicting parameters of clinical outcome, we performed acute haemodynamic evaluation on 23 pts (16 males, 72±13 years old) with cardiomyopathy of any etiology at the time of BiV implantation. All pts were in NYHA class III/IV despite optimal medical treatment, with a mean left ventricular ejection fraction (LVEF) of 23%±6 and QRS duration of 192±26 ms. During system implantation, systemic and pulmonary blood pressures were monitored before and 15 minutes after BiV was turned on, in order to evaluate systolic right and left pre-ejection periods and right and left ejection times. Interventricular delay (ID) was calculated as the difference between left and right pre-ejection period and increases proportionally with the severity of interventricular desynchronization. Evaluation of cardiac performance was done before and one week after implantation by echocardiography. After 15 minutes of BiV, a significant decrease of ID was observed (from 72±39 ms to 19±29 ms; p <0.001). At seven days, overall LVEF by echocardiography improved by more than 50% (from 23%±6 to 35%±7, p <0.001).



ID correlates with EF.

When expressed as magnitude of percentage decrease, ID calculated during acute haemodynamic evaluation, linearly and significantly correlates with the percentage increase of LVEF (r=0,771) (figure), suggesting that the degree of ID reduction predicts the outcome in short term period.

P2170 The degree of acute QRS shortening during cardiac resynchronization therapy is predictive of clinical improvement at long-term follow-up

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The response to cardiac resynchronization therapy (CRT) with biventricular pacing (BiVP) in pts with chronic heart failure (CHF) and atrio-ventricular and/or intra-ventricular dissynchrony is poorly predictable. We evaluated the role of demographic, ECG and pacing-related variables as clinical improvement predictors at long-term follow-up (mean: 19.3±7.4 mos; range: 6-34) in 36 consecutive pts (32 m, mean age 68±6 yrs) submitted to CRT because of drug-refractory CHF (NYHA class: III-IV), left ventricular (LV) ejection fraction (EF) < 35% (mean: 23.7±5.4%) and QRS duration > 150 ms (mean: 174±22 ms). In all pts the lateral LV wall was chronically paced through unipolar leads placed in coronary sinus (CS) tributaries. The right ventricular stimulation was performed in all cases from the apex. Mean right-to-left ventricular electrogram (RV-LV) delay measured 101±37 ms.
Methods and Results: Responders (R) were considered those pts fullfilling all the following criteria: > 1 NYHA class reduction, > 30% improvement of Minnesota score and 6-min walk distance, no further hospital admission for CHF during follow-up. Twentyfive pts (69%) were R. At univariate analysis, they significantly differed from non R pts because of a shorter paced QRS duration (131±6+17.8 vs 144.5±13.7 ms; p <0.04), and a greater BiVP-induced QRS reduction (Delta%) with respect to baseline (23.9±12.9 vs 14.2±10.1; p <0.03). Conversely, pt age, sex, CHF etiology, baseline NYHA class, Minnesota score and 6-min walk distance, prevalence of 1st degree atrio-ventricular block, permanent atrial fibrillation, LV pacing lead position within CS tributaries (antero-lateral, lateral or postero-lateral), and RV-LV delay were not significantly different in the 2 groups.
Conclusions: The BiVP-induced acute shortening of QRS duration significantly predicts the long-term response of CHF pts to CRT obtained through lateral LV wall stimulation.

P2171 Sensitivity and specificity of using QRS duration to predict chronic benefit in heart failure patients with cardiac resynchronization therapy

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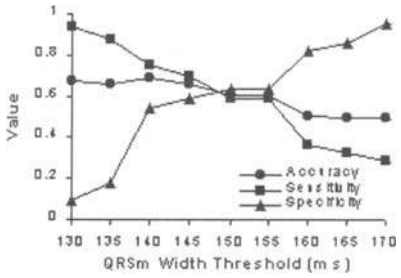
Cardiac resynchronization therapy (CRT) has been shown to provide acute and chronic benefit to heart failure patients with interventricular conduction delay. Baseline maximum QRS duration (QRSm) has been widely used as a criterion to select heart failure (HF) patients for cardiac resynchronization therapy (CRT). The efficacy of QRSm to predict chronic benefit has not been analyzed. The aim of this study was to determine the sensitivity, specificity and accuracy of QRSm to predict chronic hemodynamic benefit.
Methods: Seventy-one heart failure patients from the PATH-CHF II clinical study (NYHA Class II-IV, QRS duration > 120 ms) with complete pairs of peak VO2 (pVO2) were analyzed. All patients received CRT for 3 months. Chronic benefit was measured by changes in pVO2 during exercise over the intrinsic baseline. Sensitivity, specificity and accuracy measures were calculated for several QRSm thresholds.
Results: Accuracy was highest (69%) at QRSm of 140 ms. At this threshold, the sensitivity and specificity were 76% and 55%, respectively.



Conclusions: QRSm is useful not only in screening patients for CRT, but also in predicting chronic benefit from CRT.

P2172 The use of tissue Doppler imaging to predict improvement of left ventricular ejection fraction after biventricular pacing

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Background: Recent studies showed that biventricular (BV) pacing results in improvement of systolic left ventricular (LV) function, functional status and well being of patients with congestive heart failure. Tissue Doppler imaging (TDI) by echocardiography allows non-invasive, quantitative assessment of long-axis function with measurement of peak systolic velocity timing in relation to electrical activity. The aim of the present study was to evaluate whether improvement in LVEF post-pacing can be predicted in patients with heart failure using TDI.
Patients and methods: 25 patients with dilated cardiomyopathy (11 ischemic) were included. Patients had LVEF <35%, were in NYHA class III/IV with a QRS duration >120 ms. A routine 2D echo and TDI were performed on the day before and the day after implantation. LVEF was assessed using the biplane Simpson's method; improvement of LVEF 5% post-pacing was considered significant. From TDI, the following parameters were assessed: peak systolic velocity (PSV) and time interval from onset of QRS to PSV (TPV), and the septal to lateral delay in time to PSV. Moreover, TPV was assessed in 4 regions (anterior, inferior, lateral, septal), and an LV asynchrony score was derived from these measurements by averaging the TPV from all 4 regions.
Results: LVEF improved by 9±9% following pacing (from 22±5% before pacing to 31±10% post-pacing); 17 patients improved LVEF 5% or more. The change in PSV after pacing in the septal and lateral regions related significantly to the change in LVEF post-pacing. The change in asynchrony score (before vs post-pacing, indicating resynchronisation) was related to the change in LVEF ($y=120x+5.6$, $r=0.79$, $P<0.01$). Using a cut-off value in septal to lateral delay of $^{3}60$ ms gave a sensitivity of 82% and a specificity of 88% to predict improvement of LVEF post-pacing.
Conclusion: TDI allows evaluation of resynchronisation and may be used to predict improvement in LVEF post-pacing: assessment of septal to lateral delay in patients eligible for BV pacing can accurately predict which patients will improve in LVEF post-pacing and can be used for screening.

PREDICTORS OF ATHEROSCLEROSIS

P2173 In-stent restenosis is associated with progression of native coronary artery plaques

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Background: Although stenting leads to further reduction of restenosis, its effects on the progression of coronary artery disease are unclear. In the present retrospective study (1999-2001), we sought to identify lesional and procedural determinants that allow the prediction of in-stent restenosis (ISR) and/or of plaque progression, and that prove a possible relation between both forms of accelerated arteriosclerosis.
Methods: A total of 133 coronary target lesions of 100 patients treated by stent implantation was evaluated at the 6±2 month follow-up for ISR (defined as >50% diameter stenosis) and progression (defined as >20% increase of stenosis) of untreated coronary plaques (>30% stenosis) by use of quantitative coronary angiography. Clinical, angiographic and procedural determinants were analyzed for prediction of ISR and/or plaque progression.
Results: ISR >50% was seen in 60 of 133 (45%) cases categorized in focal (IB 15.7%, IC 23.6%, ID 13.5%) and diffuse ISR type (II 29.2%, III 13.5%, IV 4%). Longer lesion length (1.5±0.5 vs. 1.1±0.6; P=0.038), increased number of inflations (3.3±1.6 vs. 2.7±1.2; P=0.035), cumulative inflation time (P=0.046) and presence of diabetes (22 vs. 10%; P=0.048) were predictive of ISR. Within the same time window, angiographic progression was observed in 10 of 72 (13.9%) previously untreated lesions. Of note, plaque progression was influenced by the presence of ISR (P=0.044), since 9 cases were found associated with ISR, 5 of them with the focal and 4 with the diffuse type. Significant regression of plaques was not observed. In addition, the number of implanted stents (1.5±1.2 vs. 0.98±0.53; P=0.026) revealed significant relationship for occurrence of native plaque progression, whereas patient characteristics, medication and several preprocedural angiographic variables did not.
Conclusions: Our data demonstrate that procedural determinants of stent implantation/angioplasty may determine the long-term local result. Number of implanted stents and occurrence of ISR apparently favour the progression of preexisting mid-grade plaques. Conversely, these observations suggest a systemic intrinsic factor that propagates accelerated arteriosclerosis.

P2174 Hyperhomocysteinaemia is independently predictive of severity and extent of coronary artery disease

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Background: Homocysteine is an emerging risk factor, associated with atherogenesis and increased risk of cardiovascular diseases. However, the direct relationship between homocysteine and the severity and extent of coronary atherosclerosis in coronary artery disease (CAD) patients has not been well established.
Methods: 631 consecutive CAD patients (83% male), aged<70 years with angiographically documented coronary disease (>50% luminal stenosis in >=1 vessel) were studied. Severity and extent of CAD were evaluated by modified Gensini score. Total plasma fasting (>12 hour) homocysteine (tHcy) collected at angiography was measured by immunoassay (IMx), and compared in mild to moderate CAD (score<22, n=428) and severe CAD (score >22, n=208) of matched age and gender.
Results: The 2 CAD groups were similar in smoking status (64%), body mass index, blood folate, vitamin B-12, glucose and lipid profiles and prevalence of diabetes mellitus. Vitamin B-12, tHcy, creatinine and prevalence of hypertension were significantly higher in severe CAD. On multivariate logistic analysis, hyperhomocysteinaemia (>=10μmol/l) (odds ratio=1.6; 95% CI=1.2-2.4; p=0.006) and elevated creatinine (odds ratio 2.0; 95% CI=1.2-3.3; p=0.006) were independently associated with severe CAD after adjustment for traditional coronary risk factors.

Clinical Parameter of CAD Patients

	Mild-to-Moderate	Severe CAD <n=208>	p-Value
Age (yr)	58.6±8.3	59.2±8.9	0.364
Coronary Score	14.2±5.1	30.3±6.4	0.0001
Hypertension (%)	50.9	60.6	0.022
Diabetes (%)	25.5	31.7	0.097
Dyslipidaemia (%)	33.9	36.6	0.672
Body Mass Index(Kg/m^2)	24.7±3.4	25.0±3.3	0.424
LDL-cholesterol (mmol/l)	2.6±1.5	2.8±1.6	0.591
Folate (nmol/l)	24.7±1.5	25.0±1.5	0.681
tHcy (umol/l)	9.9±1.4	10.8±1.4	0.007
Vitamin B-12 (pmol/l)	293.2±1.6	269.8±1.7	0.036
Creatinine (umol/l)	92.2±21.6	98.4±21.4	0.001

Conclusions: Hyperhomocysteinaemia is an independent determinant of severity and extent of atherosclerosis in CAD.

P2175 The relationship between wall thickness and shear stress in coronary arteries of patients

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Background Atherosclerosis preferentially develops at average low shear stress locations. Shear stress controls lumen dimensions under physiological variations. We hypothesized that maintenance of lumen dimensions by shear stress control prolongs selective accumulation of plaque at low shear stress predilection locations only in early atherosclerosis, restricting the presence of an inverse relation between wall thickness and shear stress to this stage. Therefore, loss of lumen preservation and shear stress increase will change the relations between wall thickness and shear stress.

Methods and Results: In 14 patients, interventionally treated for coronary lumen narrowing, an angiographically normal artery (stenosis <50%) was investigated with ANGiography and ivUS (ANGUS) to provide 3D lumen and wall geometry. Selection of segments >5mm length in between side branches yielded 25 segments in 12 patients. Shear stress at the wall was calculated by computational fluid dynamics using a validated finite element software package (Sepran). Per segement shear stress and wall thickness data were measured at the same 16 different circumferential locations and averaged in the longitudinal direction. Linear regression analysis was used to relate wall thickness (WT) to shear stress (SS) (WT=a+b*SS). Wall thickness normalized to lumen diameter (WTn) <0.2 was defined normal. Largest arc of normal WTn defined reference (ref) cross sections. Lumen area (LA) defined area stenosis (AS): (LAref-LA)/LAref*100%. Media bounded area (MBA) defined vascular remodeling: (MBA-MBAref)/MBAref*100%. Average AS (ASav) <10% defined preserved lumen.

For the preserved lumens (n=11, ASav=1.7%, vs.0%: p=NS), wall thickness and shear stress were inversely related (slope (b):-0.00046 ± 0.00055 m^3/N, $p<0.05$) and vascular remodeling was positive (7±9%, vs. 0%: $p<0.05$). For the group showing lumen narrowing (n=13, ASav=18%±6%, vs. 0%: $p<0.05$), wall thickness and shear stress were not related (slope (b): 0.00019 ± 0.00052 m^3/N, p=NS) and vascular remodeling was absent (-3±6%, vs.0%: p=NS).

Conclusion These data show for the first time in human coronary arteries, that the presence of an inverse relationship between wall thickness and shear stress is related to lumen preservation and compensatory vascular remodeling and is absent with lumen narrowing.

P2176 Mediterranean diet phytochemicals inhibit endothelial activation through interference with redox-sensitive transcription factors

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Epidemiological studies suggest that Mediterranean diets reduce the risk of cardiovascular disease. Monocyte adhesion to the endothelium is crucial in early atherogenesis, and redox-sensitive mechanisms are involved. The aim of our study was to evaluate whether typical Mediterranean diet phytochemicals affect endothelial leukocyte adhesion molecule expression and monocyte adhesion.

Methods and Results: We studied several phenols in Mediterranean foods, including oleuropein, hydroxytyrosol, tyrosol, and resveratrol, with or without antioxidant activity. Compounds (1-100 micromol/L) were incubated with human umbilical vein endothelial cells (HUVEC) for 30 minutes, followed by coincubation with bacterial lipopolysaccharide or cytokines to trigger adhesion molecule expression. Only oleuropein, hydroxytyrosol and resveratrol, possessing a marked antioxidant activity, reduced monocytoid cell adhesion to stimulated endothelium. This correlated with the inhibition of Vascular Cell Adhesion Molecule-1 (VCAM-1) mRNA and protein expression, assessed by Northern analysis and cell surface enzyme immunoassay, respectively. The inhibition of VCAM-1 was paralleled by reduction in the activation of the redox-sensitive transcription factors Nuclear Factor-kappaB (NF-kappaB) and Activator Protein–1 (AP-1), at electrophoretic mobility-shift assays. Trasfection studies using various VCAM-1 gene promoter constructs confirmed that phenolic antioxidants repressed VCAM-1 gene transcription, in part by inhibiting NF-kappaB. E-Selectin and intercellular adhesion molecule-1 (ICAM-1) expression were similarly inhibited, indicating a generalized effect on endothelial cell activation.

Conclusions: Mediterranean diet phytochemicals possessing antioxidant activity may inhibit early events in atherogenesis modulating endothelial gene expression, and can thus be exploited pharmacologically.

P2177 Elevated plasma levels of lipid peroxidation are associated to an early onset of UA

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Atherosclerosis (ATS) in humans is associated to increased production of free radicals: particularly, an accelerated lipid peroxidation and lipoxidative aging of proteins in the vascular wall has been demonstrated in pts with ATS.

Since age is an established determinant of levels of oxidative stress in subjects without CV disease and influence pathological changes in the redox balance, we studied the extent of oxidative damage in pts with recent unstable angina (UA) according to different age of onset.

We compared EDTA plasma levels of malondialdehyde (MDA), assayed by HPLC method, in 40 male pts with early (age <56) or late onset (age >64) of UA. A control group (Controls) of healthy subjects (n=35) similarly divided by age was also enrolled for the study.

Pts with UA were characterized by more elevated levels of lipid peroxidation products than Controls (1,6 ±0,7 vs 1,1±0,3 nmol/ml $p<0.0001$).

Furthemore early onset UA pts showed higher MDA levels when compared to late onset UA pts.

Traditional risk factors for ATS were not significantly different between pts with early and late onset of UA (see table). Moreover, none of the risk factors considered showed significant correlation with oxidative stress.

	Early UA	Late UA
MDA, nmol/ml	1.8±0.1*	1.4±0.1
BMI, kg/m^2	27.2±0.7	25.7±0.7
HDL, mg/dl	38.8±1.9	39.9±1.5
LDL, mg/dl	128.0±10.8	127.7±8.3
Von Willebrand Factor, %	141.5±22.6	195.5±27.3
Fibrinogen, mg/ml	386.0±27.8	415.2±22.8
Family Hx ATS, %	63	54
Hx Dyslipidaemia, %	86	75
Hx Hypertension, %	67	64
Smokers, %	58	40

Characteristics of Patients with Early UA and Late UA. Mean ± S.E; *$p<0.01$ vs Late UA.

Intrestingly, while MDA levels increase as a function of age in Controls, this trend whose reversed in UA pts.

Elevated levels of MDA in pts with early UA point to the relevance of oxidative mechanism for development of accelerated coronary atherosclerosis.

P2178 High body iron stores predispose for early vascular modifications in b-thalassemia major patients

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Although previous studies have been reported that increased serum ferritin levels were associated with an excess risk of acute myocardial infarction, several questions regarding the relation of increased body iron stores with the atherosclerotic process remain unresolved.

Methods: For this purpose, we investigated the relation of early carotid atherosclerotic changes to body iron status on B-Thalassemia major patients, a population with chronic iron overload. Intima-media thickness (IMT) of the common carotid artery (CCA) was evaluated by high resolution B-mode Ultrasonography (Biosound 2000 II Sa) in 45 B-Thalassemia major patients (mean age 16±4 years). Our subjects were free from any known risk factors for cardiovascular disease. Body iron status was assessed by the mean serum concentration of ferritin in the last five years. The findings were compared to those obtained from 20 age and sex matched normal individuals.

Results: IMT of CCA in B-Thalassemia patients was 0.78±0.1 mm while in normal subjects was 0.54±0.2 mm ($p<0.001$). Mean serum level of ferritin in the last five years in the B-Thalassemia patients was 2720±1980 ng/ml and in normal subjects was 105±45 ng/ml ($p<0.001$). There was a strong positive correlation between IMT of CCA and level of ferritin in B-Thalassemia group ($r=0.82$, $p<0.005$).

Conclusion: The IMT of the CCA increased in proportion to the increased serum levels of ferittin. These data provide evidence that the body iron status plays an important role in the progress of early atherosclerotic changes. However, further studies are required to investigate the effects of multiple blood transfusions to cerebrovascular complications associated with B-Thalassemia major patients.

P2179 Characteristics of coronary patients with a family history of atherosclerotic disease

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Background: Family history of atherosclerotic disease increases the risk of coronary atherosclerosis (CA). Therefore, the risk factor profile of coronary patients with a family history of atherosclerotic disease is of particular interest.
Methods: We investigated 641 consecutive patients undergoing coronary angiography. Of these patients, 219 had 1, and 101 had 2 or more first degree relatives with atherosclerotic disease (single and multiple family history, respectively); 321 patients had no first degree relative with atherosclerotic disease (no family history).
Results: Among patients with single and multiple family history, the prevalence of significant CA (defined as the presence of stenoses >= 50%) was not increased compared to patients with no family history (60% and 65% vs. 60%; p=n.s.). There were more women (35% vs. 25%; p=0.008 and 48% vs. 25%; p<0.001) and fewer smokers (54% vs. 68%; p=0.004 and 52% vs. 68%; p=0.003) in these groups. Compared to patients with no family history, mean total cholesterol (227 vs. 216 mg/dl; p=0.048), HDL cholesterol (52 vs. 47 mg/dl; p=0.008), apolipoprotein A1 (155 vs. 144 mg/dl; p=0.002), and median Lipoprotein(a) values (26 vs. 13 mg/dl; p=0.004) were significantly higher in patients with multiple but not in those with single family history.
Conclusions: Among patients referred to coronary angiography, CA is not more prevalent in patients with a family history of atherosclerotic disease than in those without a family history. Patients with multiple, but not with single family history exhibit elevated serum levels of both markers of increased atherosclerotic risk (total cholesterol, lipoprotein(a)), as well as, surprisingly, markers of decreased risk (HDL cholesterol, ApoA1).

P2180 Long-term effects of diet and exercise on obesity-related vascular dysfunction in children

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Background: Obesity in children is independently associated with arterial endothelial dysfunction, a key event of atherogenesis. This is partially reversible with diet control, or more so with combined diet control and structured exercise programme for 6 weeks. However the longer-term effect of these regimens has not been documented.
Methods: 82 obese children (age 8-11 year, body mass index >23) randomized to 6-week diet control or diet plus exercise programme, were followed up for 1 year. Of the exercise group, 22 consented to continue weekly exercise programme, and 19 children pulled out at 6 weeks but continued 2-monthly diet monitoring programme, together with the original 41 diet only children. Brachial artery flow-mediated dilation (FMD, endothelium-dependent) was assessed by high resolution ultrasonography at baseline and 1 year.
Results: Significant improvement with near normalization of FMD (from 6.9±1.5% to 8.6±1.8%; p<0.001) was seen in children continuing exercise, less so in children who pulled out (from 6.7±2.3% to 7.4±2.5%; p=0.025) but not in children on diet control only (6.9±2.0% to 7.1±1.5%; p>0.5). There was significant improvement in waist-hip ratio (W/H ratio), and body fat content (p<0.005) but not body mass index in all 3 groups, but improvement in low density lipoprotein cholesterol (from 3.0±0.9mmol/l to 2.7±1.0mmol/l; p<0.005), high density lipoprotein cholesterol (from 1.2±0.3mmol/l to 1.5±0.3mmol/l; p<0.0001) and fasting insulin levels (from 156±101pmol/l to 118±74pmol/l; p<0.0001) in exercise group only. On multivariate analysis, exercise training were independently correlated to long-term improvement in FMD (partial R=0.47; F value=4.2; p=0.002).
Conclusion: Obesity-related vascular dysfunction in otherwise healthy young children is reversible at 1 year with diet plus regular exercise, less so in those who gave up exercise programme, but not with diet control only.

P2181 Pulse-wave velocity in individuals with one or two parents afflicted with coronary artery disease – A comparative study

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Purpose: To compare the Pulse Wave Velocity (P.W.V.) in subjects with negative family history of coronary disease and individuals with a family history of one or two parents afflicted by coronary artery disease.
Method: Arterial wall elasticity was determined indirectly by P.W.V. using an electronic device which recorded the left external carotid and left dorsalis pedis pulses simultaneously with a single lead ECG. The time delay between the two pulses is computed automatically. A faster P.W.V. would indicate decreased arterial wall elasticity.
Materials: A total of 108 clinically asymptomatic subjects, of average heights, non obese, with normal blood pressure and ECG in sinus rhythm and normal blood sugar and lipid profiles were studied. There were 38 males and 70 females. Of these 108 individuals, 63 had a negative family history of coronary artery disease(CAD), 32 had one parent suffering from CAD and 13 had both parents with CAD.
Results: The mean time of PWV among the subjects whose parents do not have coronary artery disease was 0.1613 sec. (Min.-0.10 & Max.-0.21 sec.) For the individuals with only one parent suffering from CAD the mean time of PWV was 0.1553 sec. (Min. 0.10 sec. and Max. 0.21 sec.); while those with both parents afflicted with CAD, the mean time of PWV was 0.1354 sec. (Min.- 0.10 sec. and Max. - 0.16 sec.) These differences in time are statistically significant. It is evident that the individuals without family history of CAD have a longer time of PWV compared to the subjects with family history of CAD. Interestingly, when we subdivide the latter group into those with one afflicted parent and two afflicted parents, we note that the latter has a significantly much slower time of PWV compared to the former. If we assume that decreased time of PWV indicates decrease of arterial wall elasticity and therefore increased risk of development of CAD, then individuals with only one afflicted parent are at lower risk compared to those with two afflicted parents.
Conclusion: Subjects without any history of coronary disease have lower risk of developing coronary artery disease. Individuals with two parents afflicted with CAD have a higher risk of developing CAD compared to those who have only one afflicted parent.

P2182 Sequential analysis of the low density lipoprotein receptor and apolipoprotein B genes of hypercholesterolemic patients from Central Europe

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Familial hypercholesterolemia (FH) is an autosomal dominant disorder caused by mutation in the low density lipoprotein receptor gene (LDLR). Several different mutations of the LDLR gene were identified.
The purpose of the study was to evaluate LDLR mutations in patients with hypercholesterolemia in a Central European population. We analyzed the LDL receptor gene using the single-strand conformation polymorphism (SSCP) and direct sequencing technique. The range of serum cholesterol and LDL-cholesterol was 250-450 and 200-400mg/dl in FH patients. In a screening of the LDLR gene mutations of 54 consecutive patients with familial hypercholesterolemia, we discovered new point mutations in 18 exon: one-nucleotide deletion (Asp2731), thirteen-nucleotide deletion (Val2734), C2623A causing Leu850Ile, T2786C, G2728A. Mutations was also located in three different exons (4,7,8); C518G causing a Cys152Trp in exon 4, T1012A causing Cys317Ser in exon 7 and T1102C causing Cys347Arg in exon 8. The mutation in exon 4 and 7 was previously reported in a compound heterozygote for familial hypercholesterolemia.
FH can be caused not only by defects in the LDLR but also by mutation in apolipoprotein B causing decreased LDLR binding affinity, so called familial defective apolipoprotein B (FDB). Three different missense mutation in 26 exon of ten patients were found: Pro2712Leu substitution, Arg3500Gln leads to a defective binding of apolipoprotein B to the LDL receptor and a novel point mutation 3532Ile.
Since novel LDLR and lipoprotein B mutations were found, we conclude that genetic determination of FH is related to the population studied. Functional importance of the mutations in patients with FH remains to be established.

P2183 Superiority of amlodipine over enalapril in reversing carotid artery intima-media thickening in hypertensive patients

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Objective: Intima-media thickening (IMT) of the common carotid artery (CCA) predisposes to the development of atherosclerosis and has been shown to correlate with coronary events and stroke. The multicenter double-blind Amlodipine Regression Study (ARES) was designed to compare the effect of the long-acting dihydropyridine calcium antagonist amlodipine (A) with that of the ACE-inhibitor enalapril (E), administered for a 2-year treatment period, on CCA-IMT in hypertensive patients (HP).
Methods: 218 HP aged 35 to 75 y. with sonographically proven CCA-IMT (far wall) of the leading side => 0.8 and =< 1.5 mm were randomly assigned to receive either A (5-10 mg/d) or E (10-20 mg/d). HCTZ was added if required to achieve blood pressure (BP) control. Ultrasonography was performed at baseline and after 12 and 24 months. Outcome results are available for 92 HP treated with A and 97 PH treated with E.
Results: After 24 months of treatment BP was reduced similarly by A and E. CCA-IMT had decreased by 0.11 mm to 0.76 mm in the A-treated group, but by only 0.08 mm to 0.81 mm in the E-treated group ($p<0.05$ for difference between treatments). Regression of CCA-IMT of 0.1 mm or more was observed in 68,5% of A-treated but in only 49,5% of E-treated HP. No correlation between fall in BP and changes in CCA-IMT was observed.
Conclusion: 2 years of effective antihypertensive treatment based on A is superior to that based on E in reversing CCA-IMT of HP indicating that A may have a more favourable effect on atherosclerosis development than E. The absence of a correlation between the fall in BP and the decrease in CCA-IMT suggests that mechanisms in addition to BP reduction might have contributed both to regression of the CCA wall lesions and to the difference in treatment effects between A and E.

P2184 Global fibrinolytic capacity in coronary artery ectasia

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Objective: Global fibrinolytic capacity (GFC) is a new, easy and reliable technique for evaluating the effectiveness of the entire fibrinolytic system. Current literature suggests that ectatic coronary arteries are subject to thrombus formation and distal microembolization. We invastigated GFC and other hemostatic parameters in patients with coronary ectasia.
Methods: Twenty-five patients with coronary ectasia (14 men, 11 women, mean age:58.4±8 years) and 25 control subjects with angiographically documented normal epicardial coronary arteries (13 men, 12 women, mean age:56.3±9 years) were enrolled in the study group. Patients who have diabetes mellitus, hyperlipidemia, hematologic disorders, hepatic or inflammatory diseases and patients with a history of thromboembolic events were not included in the study group. None of the patients with coronary artery ectasia had a history of previous acute Q-wave or Non-Q wave myocardial infarction (MI).
Results: There was no significant difference between two groups with regard to the age, sex and body mass-index. D-Dimer and GFC levels in patients with coronary ectasia were significantly higher than those of the control group (0.67±0.56 vs 0.41±0.26, p=0.04; 4.61±2.1 vs 3.14±2.11, p= 0.017; respectively). There were no significant differences between the two groups with regard to prothrombin time and activated partial thromboplastin time (p=0.48, p=0.068, respectively). Antithrombin III, Fibrinogen, Protein C and Protein S levels were also similar in both groups (p=0.42, p=.0.68, p=0.23 and p= 0.31, respectively).
Conclusion: The results of this study suggests that the micro-thromboembolic events in patients with coronary ectasia may contribute to the activation of fibrinolytic system and this phenomenon may cause increase in the levels of D-Dimer and GFC. Increased fibrinolytic activity might have a protective role in these patients otherwise prone to acute ischemic events.

LIPID-LOWERING DRUGS

P2185 Statins increase the expression of collagen I receptors in humanen VSMCs

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3-Hydroxy-3-Methylglutaryl Coenzym A Reductase (HMG-CoA) inhibitors have direct vascular effects that contribute to plaque stability. In the present study we demonstrate that the HMG-CoA reductase inhibitors atorvastatin and pravastatin augment the adhesion of human (HSMCs) and rat aortic smooth muscle cells (RASMCs) to collagen I via induction of alpha2beta1-integrin receptors. Atorvastatin (0.1 μM) increased the adhesion of HSMCs to collagen I up to 2-fold ($p<0.01$) and pravastatin (1.0 μM) up to 1.8-fold ($p<0.01$) after treatment for at least 24 hours. This increase in adhesion was concentration-dependent and was observed for treatment periods from 16 to 72 hours. Inhibition of isoprenoid synthesis with mevalonate and geranyl-geraniol prevented the statin-induced effect on human and rat VSMCs. Flow cytometry revealed an increased expression of alpha2- and beta1-integrins after treatment with atorvastatin (0.1 μM) at 24 and 48 hours. Atorvastatin increased levels of beta1-integrin mRNA after 12 and 24 hours treatment in HSMCs, which was inhibited by mevalonate. Furthermore, atorvastatin (0.1 μM) and pravastatin (1.0 μM) inhibited chemotaxis of HSMCs on collagen I, which was also reversed by mevalonate treatment. In contrast, inhibition of beta1-integrins with a specific antibody nearly doubled ($p<0.01$) the rate of chemotaxis.
These data indicate that the chemotactic activity in HSMCs is inhibited in part by upregulation of alpha2beta1-integrin receptors. The present study indicates that HMG-CoA reductase inhibitors increase cell-matrix interaction with collagen I via induction of alpha2beta1-integrins and increased adhesion to collagen I.

P2186 Pre-operative simvastatin therapy improves resting myocardial blood flow after CABG

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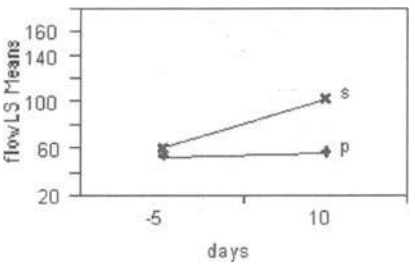
Introduction: Prior studies have demonstrated improved cardiovascular outcomes after initiation of lipid-lowering therapy. We hypothesized that pre-operative simvastatin therapy would be associated with improved myocardial blood flow following CABG.
Methods: In this prospective double blind study, patients with 3-vessel disease (CAD) were randomized to simvastatin 40mg or placebo (4 patients in each arm). Patients underwent myocardial flow imaging by PET scan 5±1 days pre-CABG and at 10+1days post-CABG. No change in medical therapy was made. All patients were started on simvastatin therapy after second PET scan. Total duration of therapy was for 15±1 days. 64 regions of myocardium were analyzed.
Results: The mean number of coronary bypass conduit per patient was 4±1. Baseline characteristics were similar between the groups. All the other variables including venous vs. arterial conduits, concurrent drug therapy, bypass time, cross clamp time and number of vessel bypassed were not significantly different between the two groups. There was no significant difference in flow between the two arms pre-CABG. While flow did not improve following CABG in the placebo arm (delta 2.9 ml/100gm/min, 95% CI. -6.3, 12.1 p=NS), flow in the simvastatin arm did improve significantly (delta 41.3 ml/100gm/min, 95% CI. 32.1, 50.5 $p<0.00001$).



Legend: p=placebo s=simvastatinstatin and myocardial flow.

Conclusion: Administration of simvastatin before CABG was associated with a significant improvement in myocardial blood flow on PET scan whereas placebo administration was not. A potential mechanism includes a reduction in reperfusion injury. While provocative, these findings require further confirmation in large number of patients and the relation to clinical events require further evaluation

P2187 Sevelamer: a new synthetic polymer for haemodialysis patients with antiatherosclerotic properties

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Background: Patients affected by end-stage renal disease (ESRD) demonstrate extremely high cardiovascular morbidity and mortality. Abnormal calcium and phosphorus metabolism as well as abnormalities of lipid metabolism appear to be related to such poor prognosis. Sevelamer (SVL) is a non-absorbed polymer indicated for phosphorus chelation in ESRD that might also have other antiatherosclerotic properties.
Method: 200 ESRD patients undergoing maintenance hemodialysis were randomized to SVL or traditional calcium salts (CaS) as treatment for hyperphosphatemia. Serial measurements were made during one year of follow-up for the following parameters: coronary artery calcium score (CCS), a marker of atherosclerosis, by electron beam tomography (EBT); serum lipids and high sensitivity C-reactive protein (hs-CRP).
Results: At the end of one year the CCS progressed significantly in CaS but not SVL treated patients (median change 25% vs 6%; p=0.02). The following variables decreased significantly in the SVL treated patients: total cholesterol (- 41 mg/dL, p<0.0001), LDL (-38 mg/dL, p<0.0001), ApoB (-25%, p<0.0001) and hs-CRP (-1 mg/L, p<0.05) while ApoA increased significantly (+3%, p<0.04). No change was noted for tryglycerides, HDL or Lp(a) with SVL. All serological variables remained unchanged in CaS patients during the course of the study.
Conclusions: SVL is a new non-absorbed polymer with potentially useful antiatherosclerotic properties. This drug may offer an important advantage over other therapies currently employed for hyperphosphatemia in ESRD by favorably altering lipoproteins and reducing arterial inflammation.

P2188 Effect of statin therapy on arterial elasticity in dilated cardiomyopathy

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Patients with dilated cardiomyopathy (DCM) have depressed left ventricular (LV) function. Decreased arterial elasticity rises LV afterload and leads to progression of heart failure in such group of patients. Pulse wave velocity (PWV) provides an indirect, non-invasive measurement of the mechanical properties of arteries. Statins by influence on migration and proliferation of smooth muscle cells may improve arterial elasticity. Statins are recommended in the treatment of patients with coronary artery disease even in those without hyperlipidemia. However, the usefulness of statins in DCM is not established. The aim of the study was to assess the influence of statins on arterial elasticity in DCM.
Material and methods: The study group consisted of 36 pts with DCM and hypercholesterolemia. They were randomized into Group I (18 pts who received statin) and Group II (18 pts who received placebo). Groups were comparable according to demographic characteristics and treatment of DCM. Before and following 6 months of treatment PWV was evaluated using a computer system COMPLIOR-Colson. For automatic measurement of PWV pressure waveforms were digitized at rate 500 Hz for carotid-femoral distance. 10 healthy volunteers constituted a control group.
Results: PWV in control group remained unchanged following study period (7,01± 0,6 m/s initial vs 7,2 ± 0,4 after 6 months). Initial PWV in both DCM groups was similar (11,7 ± 0,8 m/s in Group I vs 12,0 ± 0,6 m/s in Group II). After 6 months PWV in Group I was significantly lower (8,5 ± 0,8 m/s, p<0,05 vs initial). In Group II PWV decreased to 11,1 ± 1,1 m/s but this value did not differ significantly from the initial measurement.
Conclusion: Addition of statin to conventional treatment improves arterial elasticity in patients with dilated cardiomyopathy.

P2189 Effects of lipid-lowering treatment with atorvastatin on endothelial function in patients with ischaemic heart failure

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Background: Previous studies have shown that endothelial function is compromised in patients with heart failure and coronary artery disease. Moreover, treatment with statins improves endothelial function in patients with hypercholesterolemia. However, the effect of statins on endothelial function and ejection fraction in patients with ischemic heart failure is not known.
Methods: In this double blind placebo controlled study, 38 patients with ischemic heart failure (32 males 6 females aged 64.8±3.4 years) were enrolled. 18 patients received atorvastatin 10mg/day (group A) while 16 patients received placebo (group B) for 4 weeks. All patients were NYHA II to IV. Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to maximal flow during reactive hyperemia. Endothelium independent flow (NTG%) was expressed as the % change from baseline to post sublingual nitroglycerin administration flow. Ejection fraction of the left ventricle was estimated with Simpson's method. All values are expressed as mean±SEM.
Results: Blood pressure, heart rate, basal forearm blood flow, NTG% and body weight remained unchanged in both groups. After 4 weeks of treatment, FMD was significantly increased in group A (from 44.2±4.4 to 96.5±12.1%, p<0.01) while remained unaffected in group B (from 46.1±6.1 to 53.5±4.0%, p=NS). Ejection fraction was also improved in group A (from 26.00±0.92 to 28.70±1.0%, p<0.05) while remained unaffected in group B (from 27.1±1.2 to 28.1±0.91%, p=NS).
Conclusions: These findings indicate that atorvastatin treatment for 4 weeks significantly improves endothelial function and ejection fraction in patients with ischemic heart failure. These findings may provide evidence for an additional effect of statins beyond lipid lowering.

P2190 The benefit of early use of lipid-lowering drugs at discharge in patients with acute coronary syndromes is greater in patients with heart failure

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The early use of lipid lowering drugs (LLD) after acute coronary syndromes (ACS) is not yet well established. The benefit of reducing cholesterol in congestive heart failure (CHF) has recently been questioned by observations of a negative relationship between cholesterol and mortality. It has therefore been suggested that it is important to maintain elevated cholesterol levels in pts with CHF. No prospective trials have yet been carried out to test the efficacy of reducing cholesterol in pts with CHF.
Methods: We assessed the impact of early LLD use at discharge from hospital after ACS on 30-day outcome among pts admitted to all 26 hospitals in Israel participating in ACSIS 2000.
Results: Among 2,131 consecutive ACS survivors, 618 pts (29%) had CHF on admission or during their hospitalization course (CHF+), and 1,513 pts did not have CHF (CHF-). LLD (99% statins) at discharge was given to 251 pts (41%) in the CHF+ subgroup, and to 853 pts (56%) in the CHF- subgroup. In both subgroups, pts discharged on LLD (LLD+) were younger, and included more often pts with hyperlipidemia (HPL), and prior revascularization (p<0.01 for all). Mean total cholesterol during the acute phase of ACS was higher in LLD+ than in LLD- pts, in both CHF+ and CHF- subgroups: 219±50 vs. 185±42 mg/dl, and 213±44 vs. 187±34 mg/dl, respectively, p<0.0001 for both). Thirty-day mortality rate in CHF+ pts was lower in LLD+ vs. LLD- pts (4.6% vs. 8.9%, respectively, p<0.05; age-adjusted OR=0.53, 95% CI 0.25-1.07), while in CHF- pts, the beneficial effect of early LLD use was smaller (0.9% vs. 1.6%, respectively, p=0.19; OR=0.86, 95% CI 0.30-2.38).
Conclusions: This observational national survey suggests that LLD given early in the setting of ACS exerts a greater short-term benefit in pts with CHF than in counterparts without CHF. Ongoing randomized trials will determine whether this striking beneficial effect is related to selection bias or to other protective effects of statins.

P2191 Effect of simvastatin on endothelial damage markers and clinical outcomes in acute coronary syndromes

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Acute coronary syndromes (ACS) are characterized by plaque inflammation, endothelial dysfunction and thrombosis. Therapeutic strategies should theoretically address to all pathogenetic mechanisms involved. In this randomized controlled study we evaluated the effects of early treatment with simvastatin (S) on markers of plaque inflammation, endothelial damage and thrombosis in 76 patients with ACS and 11 age-matched controls. Blood samples were drawn within 48 hrs from symptoms onset and 3 months after randomization into a treatment group (S 40 mg plus diet) or diet alone. C-reactive protein (CRP), thrombomodulin (TMB), t-PA, PAI-1, fibrinogen (FGN), fragment 1+2 (F1+2), vWF, and antibodies against oxidized-LDL (ox-LDL-AB) were obtained at baseline and after 3 months. There were no differences in baseline characteristics and concomitant treatments. The major adverse clinical events (MACE) considered were death, myocardial infarction, re-hospitalization for ACS. Simvastatin reduced the LDL cholesterol from 148±40 mg/dl to 92±29 mg/dl (p=0.0021); diet alone was unsuccessful in this regard (136±30 mg/dl vs 129±34 mg/dl). Simvastatin also reduced MACE from 19.4% to 10.0% (p=NS.).

Results: see the table.

	S baseline	S 3-month	p	Diet baseline	Diet 3-month	p
TMB	26±9	30±11	0.009	27±13	27±13	NS
PCR	1.05±1.64	0.22±0.23	0.00002	1.52±2.04	0.80±0.86	0.002
F1+2	2±3	5±6	0.009	6±8	5±4	NS
vWF	87±26	72±17	0.0001	90±26	75±16	0.02
ox-LDL-ab	235±208	307±230	0.002	224±120	251±125	NS
PAI-1	30±20	43±32	0.006	40±33	45±30	NS
t-PA	21±16	8±4	0.005	19±11	9±5	0.002
FGN	287±119	271±58	NS	305±121	274±68	NS

In conclusion early treament with simvastatin 40 mg in ACS results in several changes in markers of endothelial damage that are not observed in the diet group and do not appear related to inflammation. Noteworthy is the increase in TMB levels observed in the simvastatin group. The observed effects on clinical outcomes deserves further investigation in larger studies.

P2192 Prevention of nitrate tolerance by long-term treatment with statin

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Recent studies have shown that statin seems to upregulate the endothelial NO synthase pathway (eNOS) and may, therefore, enhance NO availability, a direct scavenger of O2- and an inhibitor of oxidative enzymes.

Methods: To assess whether the oxidative stress produced by an in vivo exposure to nitroglycerin (NTG) is attenuated by statins, 4 groups of normocholesterolemic rats were treated; group 1 received pravastatin (20 mg/kg/d p.o) and group 2 atorvastatin (10mg/kg/d) both for 5 weeks and the last 3 days, a cotreatment with the statin plus NTG (50 mg/kg/d, sub-cutaneous injections b i d); group 3 (NTG) received only NTG (50 mg/kg/d, b i d for 3 days) and group 4 served as control. Rings of thoracic aortas from these groups were studied in organ baths.

Results: Relaxations to NTG (0.1 nM to 0.1 mM) were determined on phenylephrine-preconstricted rings and O2- production (counts/10s/mg) was assessed by lucigenin chemiluminescence technique. In goup 3 (NTG), the concentration-response curves to NTG were significantly shifted to the right: the pD2 (-log NTG concentration evoking a half maximal relaxation) was 5.9±0.3 (n=9) vs 7.2±0.1 in group 4 (not exposed to NTG, n=9) and O2- production was enhanced (946±51 vs 617±76, P<.05). In contrast, groups 1 (n=11) and 2 (n=7) behaved as group 4 (pD2 values were 7.3±0.2 and 6.9±0.1; O2- production was 528±28 and 647±124). The protective effect on nitrate tolerance disappeared when L-NAME (an eNOS inhibitor, 100 mg/kg/d) was coadministered with NTG in groups 1 and 2. Moreover, in groups 1 and 2, before NTG exposure, aortic cGMP content, reflecting endothelium-derived NO availability, was significantly enhanced (P<.05 vs control) whereas NAD(P)H oxidase activity was decreased.

Conclusion: Long-term statin treatment protects against nitrate tolerance by counteracting NTG-induced increase in O2- production. This protection seems to involve the eNOS pathway, probably an inhibition of oxidative enzymes by enhanced NO availability.

P2193 Effects of lipid-lowering therapy with bezafibrate on endothelial function and aortic stiffness in patients with type 2 diabetes mellitus

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Dyslipidemia characterized by elevated triglyceride (TG) and reduced HDL-cholesterol (HDL-C) has been reported in patients with type 2 diabetes mellitus (DM). This study was designed to evaluate effects of bezafibrate on endothelial function and aortic stiffness. Twenty well-controlled diabetic patients (type 2) with elevated TG (TG>150 mg/dL) were randomized to receive or not receive bezafibrate (treatment group, n=10, no treatment group, n=10). By using ultrasound with a 7.5-MHz transducer, the brachial artery diameter was measured at rest and during reactive hyperemia (flow-mediated dilatation, FMD), and before and after 0.3 mg of sublingual nitroglycerin (nitroglycerin-induced dilatation, NID). And we also measured aortic PWV (pulse wave velocity) by using a non-invasive technique to evaluate aortic stiffness. These measurements were performed in 12-hour overnight fasting condition at baseline and after 12 months of the treatment. At baseline, there was no difference in lipid parameters, fasting glucose level, HbA1c, brachial artery diameters, %FMD (%increase in diameter during hyperemia), %NID (%increase in diameter after NTG), and PWV among two groups. After 12 months, triglyceride and LDL-C levels were significantly decreased, and HDL-C level was significantly increased in the treatment group (TG: -40%; LDL-C: -13%; HDL-C: +19%), but they were not changed in the no treatment group. %FMD and PWV were improved after 12 months of treatment with bezafibrate. On the other hand, %NID, fasting glucose level and HbA1c did not change after 12 months.

		Baseline	12 months	
FMD (%)	Treatment	6.1±1.2	9.9±2.0*	p<0.05
	No treatment	6.0±1.1	6.4±1.8	
NID (%)	Treatment	13.2±3.7	13.6±3.5	
	No treatment	13.0±3.2	13.4±3.1	
PWW (cm/s)	Treatment	1529±84	1125±64*	p<0.05
	No treatment	1561±76	1488±58	

Mean±SD, *p<0.01 vs Baseline.

Conclusion: Lipid-lowering therapy with bezafibrate restores endothelial function and aortic stiffness in patients with type 2 DM.FMD and PWV in patients with type 2 DM

P2194 Atorvastatin inhibition of CD40 expression attenuates CD154-mediated interleukin-12 expression in human endothelial cells

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CD40-CD40 ligand (CD154) interactions not only play an important role in an exaggerated Th1 or Th2 immune response but also in the pathogenesis of atherosclerosis. 3-Hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors (statins) exert potent anti-inflammatory effects independently of their cholesterol lowering action.

Methods: We have investigated the effects of statins on interferon g (IFNg)/tumor necrosis factor a (TNFa)-induced CD40 expression both in human cultured endothelial cells (HUVEC) and in the pre-monocytic cell line THP-1 by reverse transcription-polymerase chain reaction (RT-PCR) and Western blot analysis. Cytokine-dependent activation of transcription factors was judged by electrophoretic mobility shift analysis (EMSA). Finally, the effects of atorvastatin on endothelial cell-leukocyte interaction (parallel plate flow chamber) and CD40/CD154-mediated IL-12p40 expression (RT-PCR) were employed.

Results: Preincubation of cells with atorvastatin (10 μM) inhibited IFN-g/TNF-a-induced CD40 expression by approximately 50% at the mRNA and protein level and could not be reversed by mevalonic acid (400 μM). Moreover, EMSA revealed significant inhibition of STAT-1 and IRF-1 transcription factor translocation to the nucleus (1 h pre-incubation with statins, 3 h cytokine-incubation). Brief (1 h) pre-incubation of either cell type with atorvastatin, cerivastatin or pravastatin (1-10 μM) inhibited IFNg plus TNFa stimulated CD40 expression in these cells by approximately 50%, an effect that was also not reversed by the HMG-CoA reductase product mevalonic acid (400 μM). Furthermore EMSA demonstrated atorvastatin inhibition of the NF-kB plus STAT-1-dependent de novo synthesis of IRF-1 which governs IFNg plus TNFa stimulated expression of CD40 in these cells. Consequences of this statin-dependent down-regulation of CD40 expression in the endothelial cells were a decrease both in endothelial cell-leukocyte interaction and CD154-induced interleukin-12 expression.

Conclusions: These findings suggest that by interfering with IFNg-dependent CD40 expression in endothelial cells and monocytes, statins are capable of attenuating CD40/CD154-mediated pro-inflammatory reactions, and this may contribute to their cardioprotective action.

P2195 The effect of atorvastatin on myocardial contractile reserve assessed by tissue Doppler imaging during dobutamine stress echocardiography

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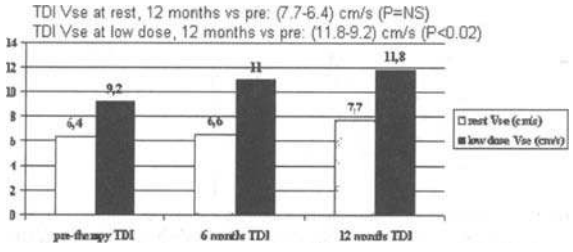
Aim: To determine the effect of atorvastatin on myocardial contractile reserve in patients with moderate hypercholesterolemia. BACKGROUND: Statin therapy has been shown to exert a beneficial effect on cardiovascular system beyond cholesterol lowering action. One of the mechanisms that have been proposed is an effect on impaired flow-mediated vasodilation.
Methods: Ten patients (age 56±12, 8 male) with peripheral vascular disease (PVD) and without a history of myocardial infarction or treatment with statins in the past were studied. All patients underwent dobutamine stress echocardiography (DSE) before the initiation of atorvastatin therapy (10mg daily) and 6 and 12 months later. Pulsed-wave tissue Doppler imaging (TDI) was performed using a six-segment model and myocardial systolic ejection velocities (Vse) were measured at rest and during low dose dobutamine infusion. There were no changes in medical therapy and no major cardiac events occurred during this period. The Student's t test was used for statistical analysis and P values <0.05 were considered statistically significant.
Results: Rest and low dose rate-pressure product (in bpm X mmHg) during DSE were 10958 and 11662 before therapy, 9240 and 10666 at 6 months and 9986 and 10740 at 12 months respectively (P=NS). Rest and low dose dobutamine wall motion score indexes as well as ejection fractions were not changed significantly. Figure 1 shows the changes in myocardial Vse at rest and during low dose DSE.



Conclusions: Atorvastatin caused a significant increase of myocardial Vse during low dose DSE in moderately hypercholesterolemic patients with PVD after 12 months of treatment. The underlying mechanism could be a beneficial effect of atorvastatin on an impaired myocardial contractile reserve.

P2196 HMG-CoA reductase inhibitor (statin) blocks VEGFR-2-mediated endothelial migration

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Statins (HMG-CoA reductase inhibitors) have been shown to reduce vascular inflammation, to increase endothelium-derived NO production, to stimulate the formation and differentiation of endothelial progenitor cells and to stimulate angiogenesis in a rabbit hindlimb model. Statins inhibit the cholesterol biosynthesis and protein isoprenylation. Isoprenylation of GTPases is necessary for intracellular trafficking, membrane association and activity. VEGF-A is a key regulator of endothelial function such as migration and cytoskeleton rearrangement through VEGFR-2 (KDR), which is controlled by activation of the GTPase Rac. The purpose of this study was to elucidate the role of statins on VEGFR-2-mediated endothelial migration.
Porcine aortic endothelial cells expressing VEGFR-2 (PAEC/KDR) were used for this study. Migration was assessed in a chemotaxis assay using a 48-well modified Boyden chamber. For action cytoskeleton analysis, actin was stained with rhodamine isothiocyanate-conjugated phalloidin and examined using a confocal laser scanning microscope. Rac activity was analysed using a PAK-1-GST pulldown assay. Membrane and cytosolic proteins were seperated using a particulate fraction assay followed by Western blot analysis.
VEGF-A-induced migration and cytoskeleton rearrangement of PAEC/KDR was significantly reduced in the presence of statins and was reconstituted in the presence of mevalonate. Analysing PAEC/KDR separated proteins into membrane and cytosolic fractions, we found an accumulation of Rac in the cytosolic fraction in the presence of different statin concentrations. Likewise, Rac activity was significantly decreased.
In conclusion, our results show that HMG-CoA reductase inhibitors can block important VEGF-A-mediated endothelial functions with implications for VEGF therapy.

P2197 Efficacy and safety of simvastatin versus atorvastatin: results of the comparative HDL-C efficacy and safety study (CHESS)

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Objectives: To assess the comparative efficacy of simvastatin 80 mg (S) versus atorvastatin 80 mg (A) on HDL-C (primary) and Apolipoprotein (Apo) A-I values and to evaluate the effects of S and A on ALT/AST and clinical GI adverse events (AEs).
Methods: In a multicenter, randomized, double-blind, parallel-dose study, 917 patients with hypercholesterolemia were treated with S or A for 24 weeks. Prespecified times for assessment of efficacy were 6/12 weeks and 18/24 weeks (mean of weeks 6 and 12 and weeks 18 and 24).
Results: S increased HDL-C and Apo A-I values significantly more than A at weeks 6/12 and 18/24 overall and across all baseline HDL-C subgroups (<40 mg/dL, >=40 mg/dL). Consecutive elevations in ALT/AST greater than 3X upper limit of normal occurred in significantly fewer patients treated with S than with A (2/453 (0.4%) versus 13/464 (2.8%), p=0.007), with a majority of elevations observed in women (S 1/199 (0.5%); A 11/209 (5.3%)). At the primary 6/12 week time point, A and S lowered LDL-C by 53.5 ± 0.6% and 45.4 ± 0.6% and triglycerides by 34.1 ± 1.4% and 25.8 ± 1.4%, respectively (p<0.001).

Mean % change in HDL-C and Apo A-1

Weeks	HDL-C	HDL-C	Apo A1	Apo A1
	S (N=436)	A (N=430)	S (N=423)	A (N=420)
6/12*	8.9 ± 0.6	3.6 ± 0.6	4.9 ± 0.7	-0.9 ± 0.7
18/24*	8.3 ± 0.7	4.2 ± 0.7	3.7 ± 0.7	-1.4 ± 0.7

*p<0.001 for S versus A

Conclusions: S 80 mg increased HDL-C and Apo A-1 significantly more than A 80 mg at weeks 6/12 and 18/24 of treatment. Significantly fewer elevations in ALT/AST occurred in patients treated with S.

P2198 Differences in the effects of fluvastatin on lipoprotein subclasses distribution and on endothelial function are dependent on triglyceride levels

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Background: The highly atherogenic small/dense LDL particles are more prevalent in those with triglyceride (TG) levels above 150 mg/dl.
Methods and Results: The present study compared the effects of fluvastatin on lipoprotein subclasses and on the endothelial function in coronary patients with plasma TG levels below and above 150mg/dl, when adjusted to LDL-cholesterol (LDL-C) levels. The study included 19 coronary patients with plasma LDL-C above 130 mg/dl after 6 weeks of NCEP step II diet. They were allocated in two groups: low TG group (TG<150mg/dl, n=13) and high TG group (TG>150mg/dl, n=6). All of them received fluvastatin 40 to 80 mg/day, titrated to bring the LDL-C below 100mg/dl, for 24 weeks. Nuclear magnetic resonance spectroscopy of plasma was used to assess the concentrations of total cholesterol (TC), TG, LDL-C, HDL-C and lipoproteins subclasses. Brachial artery flow mediated vasodilatation measurement by Doppler echography was used as an index for endothelial function. Statistical methods: Two-way ANOVA repeated measures with Scheffe's test. Low and high TG groups presented differences in TG and HDL-C levels. TC and LDL-C had no differences. After 24 weeks of fluvastatin (all comparisons are low TG vs. high TG groups), TC changed from 212±23 to 180±17mg/dl (p=0.002) vs. 222±43 to 167±28mg/dl (p=0.0007), TG from 113±25 to 119±43mg/dl (p=0.98) vs. 213±31 to 143±27mg/dl (p=0.01), LDL-C from 148±23 to 116±18mg/dl (p=0.0006) vs. 156±48 to 106±28mg/dl (p=0.0004), HDL-C from 37±7 to 40±8mg/dl (p=0.38) vs. 30±6 to 37±9mg/dl (p=0.03). Changes in lipoproteins subclasses distribution: small/dense LDL particles (L1) from 23±27 to 25±22mg/dl (p=0.99) vs. 105±67 to 19±18mg/dl (p=0.002). Endothelial function: all the cases that presented paradoxical response at the week zero in the high TG group were turned to physiological response at week 24, while there were no changes in the low TG group.
Conclusion: Only in high TG group, there were: significant decrease in the small and dense LDL subclasses (L1) concentration and improvement of endothelial function on those that presented paradoxical response before the treatment with fluvastatin.

P2199 Short-term treatment with simvastatin diminished plasma index of neutrophils degranulation

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Background: Several data suggest that simvastatin has an anti-inflammatory activity. Polymorphonuclear neutrophils (PMN) play an important role in inflammatory reaction due to their ability to release enzymes from secretory granules. Plasma levels of beta-glucuronidase, stored in azurophilic granules and lysozyme stored in both specific and azurophilic granules are used as markers of neutrophils degranulation. The aim of our study was to evaluate prospectively serum concentration of lysozyme and beta-glucuronidase in hypercholesterolemic patients treated with simvastatin.
Methods: Peripheral blood samples were collected from 19 hypercholesterolemic patients (mean serum cholesterol level 302 mg/dl) before and after 8 and 12 weeks of cholesterol-lowering therapy with simvastatin (20 mg/day). Serum lysozyme levels were decreased significantly after 12 weeks (10.9±0.5 vs 9.3±0.6 ug/ml, p=0.01) of treatment but not after 8 weeks of therapy(10.3±0.5 ug/ml, p=0.37), while beta-glucuronidase serum concentrations were significantly diminished after 8 weeks (3.9±0.8 vs 1.4±0.4 ug/ml, p=0.03) and 12 weeks of simvastatin treatment (2.1±0.6 ug/ml, p=0.02). Lysozyme and betaglucuronidase significantly correlated with plasma cholesterol concentrations (r=0.4 p=0.003, r=0.3 p=0.02, respectively).
Conclusions: Short-term treatment with simvastatin significantly reduces polymorphonuclear neutrophils degranulation markers

P2200 The effect of statin therapy on exercise induced ischaemia and endothelium dependent vasodilation in patients with cardiac syndrome-X

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Background: The pathophysiologic mechanism in cardiac syndrome-X has been suggested as an impairment in endothelial function of the coronary microvasculature, resulting in inadequate coronary flow reserve. Aim of this study was to determine whether statins have any effect on endothelial functions and exercise induced ischemia in syndrome-X.
Methods: Study population consisted of prospectively enrolled 35 patients (pts) with cardiac syndrome-X. All pts had typical exertional chest pain, positive exercise testing, and normal coronary angiograms. Pts with left ventricular hypertrophy, hypertension, diabetes mellitus, and LDL levels >150 mg/dl were excluded. Twenty pts were randomized to pravastatin(40 mg/day) for 3 months irrespective of lipid values. Endothelial functions were assessed with high-resolution vascular ultrasound(7.5 mHzprobe) which measured the changes in brachial artery diameter in response to hyperemic flow. Lipid measurements, symptom limited exercise tests(modified Bruce protocol), and vascular ultrasound images were obtained before and at the end of therapy.
Results: Baseline clinical characteristics of the groups were similar. After the treatment, LDL levels decreased significantly in the statin group (p=0.005). Brachial artery flow mediated dilatation (FMD) improved significantly in the statin group (p=0.002). Total exercise time, and time to 1mm ST depression were significantly increased after statin therapy. Ischemic ECG findings during exercise test disappeared completely in 5 (25%) pts in the statin group. Meanwhile, there were no significant changes in lipid levels, FMD and exercise test parameters in the control group.

Comparison of groups

	Pravastatin group		Control group	
	Baseline	3rd month	Baseline	3rd month
LDL(mg/dl)	121±31	97±19	116±28	119±24
FMD(%)	9.3±5.1	15.2±5.9	10.4±8.2	9.1±7.6
Total exercise time (min)	8.1±1.9	11±1.7	9.4±2.6	8.9±2.6
Time to 1mm ST depression (min)	2.9±1.6	6.1±2.2	3.3±1.2	3.1±1.6

Conclusion: Statin therapy have beneficial effects both on exercise induced ischemia and endothelial functions in pts with cardiac syndrome-X.

P2201 Clinical benefits of statin therapy initiated prior to percutaneous coronary intervention in patients with history of unstable angina pectoris

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Background: Early invasive treatment of patients with unstable angina is a currently accepted approach. Culprit atherosclerotic lesions may remain potentially vulnerable for months following the acute event, which may worsen prognosis following coronary intervention (PCI) in those patients. Further data indicate that statin therapy may passivate unstable atherosclerotic plaques. Therefore we hypothesised, that coronary plaque passivation with statins initiated prior to PCI may improve clinical outcome in terms of major acute coronary events (MACE)(MI, death, revascularisation) as well as target vessel revascularisation (TVR) in patients with potentially unstable lesions.
Methods: We prospectively assessed 168 consecutive pts (121 men, mean age 57,1±9,1) with history of unstable angina within preceding 6 months, who underwent PCI. Follow-up was available for all the patients at mean of 9,4±3,8 months. Influence on clinical outcome of classical risk factors for coronary artery disease (sex, age, BMI, smoking, family history, DM, hypertension, hyperlipidemia), number of PTCA, stents, statin therapy initiated prior to intervention, and statin therapy continued during follow-up were assessed by multivariate analysis.
Results: 82 out of 168 patients (48,8%) had been receiving statins prior to PCI whereas during follow-up 114 (67,9%) patients were on statins. During follow-up 37 pts (22%) had MACE of which 24 pts (14,3%) had TVR. Patients on statins prior to PCI had fewer MACE and TVR (table). Statin pretreatment was the strongest independent predictor of MACE (OR 0,32;95%CI 0,14-0,72;p=0,005) and TVR (OR 0,34; 95%CI 0,13-0,94; p=0,038) in a multivariate model.

	statin pre-PCI (n=82)	no statin pre-PCI (n=86)	p
TVR % (n)	9% (7)	20% (17)	0,038
MACE % (n)	12% (10)	31% (27)	0,003

Conclusions: Statin pretreatment is independently related to better mid-term clinical outcome after PCI following unstable angina. Our results suggest that pharmacological plaque passivation with statins initiated prior to coronary intervention may reduce clinical restenosis. Therefore it should be considered for all patients awaiting coronary intervention, especially in those with conceivably unstable plaque.

P2202 Use of statins is associated with improved arterial stiffness in patients with coronary artery disease

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Arterial stiffness may influence the prognosis of patients (pts) with coronary artery disease (CAD). To identify factors which affect arterial stiffness in those pts, we examined 235 pts undergoing coronary angiography for CAD (age 61.3±10.9 years, 208 men) with radial artery applanation tonometry and pulse wave analysis; augmentation index (AI) was used as an indirect index of arterial stiffness. In all pts flow-mediated dilatation of the brachial artery (index of endothelial function) and intima-media thickness of the carotid artery were also measured. AI in pts was related to peripheral systolic (r=0.26, p<0.001) and mean blood pressure(r=0.26, p<0.001) and heart rate (r=-0.539, p<0.001). Endothelial function, blood lipids, carotid artery IMT, extent of CAD (Gensini score) and BMI were not related to AI (ns). From the analysis of medication used, calcium antagonists, ACE inhibitors, beta blockers, diuretics and nitrates did not influence AI. One hundred pts were on treatment with statins; pts on statin therapy had higher percentage of previous myocardial infarction (p=0.003) and higher Gensini score (p<0.001). Pts on statins did not differ from pts without statins regarding heart rate, age, endothelial function, carotid artery IMT, ankle-brachial index, BMI, cholesterol, triglycerides, LDL and HDL-cholesterol. Systolic blood pressure was lower (116±17 vs 127±17 mmHg, p<0.001) and AI was better in the group of statins (19.1±15.2 vs 24±18.5%, p=0.038). In conclusion, pts with CAD on statin therapy appear to have lower arterial stiffness despite the more extended coronary artery disease; this effect on stiffness is independent of lipid-lowering effects; a beneficial effect of statins on arterial stiffness through reduction of the arterial pressure cannot be excluded.

P2203 Statin therapy within the initial 24 hours of acute myocardial infarction: insight into why mortality is reduced

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Background: Several observational studies have demonstrated an association between use of statin therapy during hospitalization in patients with acute myocardial infarction (AMI) and lower in-hospital mortality. No work has examined the potential clinical mechanisms for this observation. Several large randomized clinical trials remain ongoing with regard to this issue.
Methods: We analyzed 3226 patients with AMI admitted to our CCU from 1988 until 2001. Patients were divided into two groups: those receiving statin therapy (n=220) and those not receiving statin therapy (n-=3006) during the initial day of hospitalization over the study period. We included ST elevation and non-ST elevation AMI. We analyzed overall mortality and cause-specific mortality between both groups.
Results: Of the total group of patients with AMI, only 220 were given statin therapy during the initial 24 hours of hospitalization. In-hospital mortality was reduced in those receiving statin therapy (2.7%, 6/220) compared to the non-statin group (9.2%, 277/3006), p=0.001. The unadjusted odds ratio with regard to risk reduction of mortality was 0.28 (0.12-0.68). We observed no overall differences with regard to death from recurrent ischemia (3/6 vs 99/277), cardiac arrhythmia (0/6 vs 2/277), CHF (2/6 vs 46/277), mechanical complications (0/6 vs 15/277), stroke (0/6 vs 10/277) or hemorrhage (0/6 vs 1/277), p=ns. The median time to death appeared slightly longer in the statin group (132 hours, 25th percentile-75th percentile 72-168 hours) compared to the non-statin group (72 hours, 24-192 hours), p=0.3.
Conclusion: Use of a statin agent during the initial 24 hours following hospitalization for AMI was associated with reduced in-hospital mortality in our population. Additionally, the timing of death was later in those who received statin therapy compared to those not treated with a statin. The mechanism for the reduction in mortality appeared unrelated to an arrhythmogenic, ischemic or cardio-embolic mechanism. Further work is necessary to elucidate the mechanisms by which statin therapy reduce early mortality in AMI.

P2204 Dual effects of HMG-CoA reductase inhibitors on vascular endothelial growth factor synthesis

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Background: HMG-CoA reductase inhibitors (statins) exert pleiotropic effects on the vascular wall independent of the reduction in plasma cholesterol. Moreover, both pro- and anti-angiogenic activities of statins have been recently demonstrated. The aim of this study was to elucidate whether the angiogenic effects of statins are due to dose- and/or cell-dependent properties.
Methods: We investigated the effect of different concentrations (0.01 to 10 μM) of atorvastatin, simvastatin and lovastatin on the basal and induced [by IL-1β, S-Nitroso-N-acetyl-D,L-penicillamine (SNAP - an NO-donor) and lysophosphatidylcholine (LPC)] synthesis of vascular endothelial growth factor (VEGF) in human vascular smooth muscle cells (HVSMC), microvascular endothelial cells (HMEC-1) and umbilical vein endothelial cells (HUVEC).
Results: In HVSMC statins decreased the basal, cytokine and SNAP-induced release of VEGF. Additionally, statins diminished SNAP- or LPC-induced VEGF synthesis in HMEC-1. In contrast, low concentrations of statins increased intracellular VEGF protein and enhanced VEGF mRNA expression in HUVEC significantly. In addition, an in vitro assay showed increased tube formation by HUVEC after treatment with low concentrations of statins (0.1-1μM). At higher concentrations (10 μM) the proangiogenic effect of statins was no longer evident and VEGF synthesis was decreased.
Conclusion: Our data show that statins exert dual effects on VEGF synthesis. They promote the production of small amounts of this growth factor in primary endothelial cells but they inhibit the release of high amounts of VEGF by smooth muscle cells or an immortalized endothelial cell line. This dual, modulatory effect may partially explain the benefit of statins seen in large clinical trials.

INFECTION IN ATHEROSCLEROSIS

P2205 Elevated proinflammatory mediators correlate with the progression of P. gingivalis infection atherosclerosis in an ApoE (+/–) murine model

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Background: Recent studies have demonstrated that Porphyromonas gingivalis (P.g.), a pathogen implicated in periodontal diseases, is capable of accelerating atherosclerosis lesions in a heterozygote ApoE+/- mice model. However the underlying causal effect remains unknown. The purpose of this study was to correlate the time course of systemic proinflammatory markers with the progression of murine atherosclerosis.
Materiel and Method. Ten-week old, male ApoE +/- mice fed either a high-fat diet (HFD) or regular chow were inoculated intravenously with live P.g. (10 pwr(7) CFU) or vehicle once per week for 10, 14 or 24 consecutive weeks (n = 5 per group for each time point). Histomorphometry of plaque cross-sectional area in the proximal aortas, en face measurement of plaque area over the aortic trees, P.g. 16S ribosomal DNA amplification with PCR, ELISA for systemic proinflammatory proteins as interleukin 1beta (IL-1beta) and acute phase protein serum amyloid A (SAA) were performed.
Results: The level of IL-1beta and SAA was found to correlate significantly with the progression of atherosclerosis observed ApoE+/- mice fed HFD (r^2=0.80). The same profile, of elevated proinflammatory mediator was found in ApoE+/- mice fed chow diet, yet to a lesser extent (r^2= 0.69). Finally, P.g. was detected by PCR in atherosclerosis lesion only at 24 weeks.
Conclusion: The present data demonstrate that 1) atherosclerosis lesions at 10 and 14 weeks result probably from the effects of P.g-triggered systemic inflammatory processes; 2) whereas at 24 weeks atherosclerosis lesions result from the combination effect of systemic inflammatory processes as well as P.g-induced local aortic endothelial cell dysfunction. This highlights the importance of controlling the inflammatory load in the prevention of atherosclerosis lesions.

P2206 Chlamydia pneumoniae in the atherosclerotic plaques of patients with coronary artery disease. Does it have prognostic implications?

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C. pneumoniae (CP) has been implicated in the pathogenesis of coronary artery disease, but whether antichlamydial antibodies and the presence of CP in the coronary atherosclerotic tissue are related to prognosis remains unclear. This study sought to evaluate the prognostic significance of the presence of DNA of CP in the coronary atherosclerotic lesiόns of patients with unstable angina.
Methods: 76 coronary specimens from 45 patients with unstable angina undergoing bypass surgery were subjected to nested polymerase chain reaction (PCR) for CP. Antichlamydial IgG, IgA and IgM were also examined. Patients were followed during a two-year period.
Results: DNA of CP was detected in 57 (75%) of 76 atherosclerotic lesions: 39 patients showed a positive PCR result in at least one plaque. 44 (97,7%) of the 45 patients showed a positive serological result: IgG was positive in 39 (86,6%) patients, IgM in 5 (11,1%) and IgA in 42 (93,3%). At least one adverse event occurred in 21 (46,6%) of the 45 patients at two years: death in 9 (20%), recurrent angina in 12 (26,6%), revascularization in 6 (13,3%) and myocardial infarction in 2 (4,4%) patients. The composite endpoint of death, myocardial infarction, recurrent angina and revascularization at 2-year follow-up did not differ according to the presence or absence of CP in the atherosclerotic plaques or to the serologic results.

Outcome according to serology

	Free of endpoint at 2 years	p value
PCR +	5/24 (20,8%)	0.12
PCR -	1/21 (4,7%)	
IgG +	4/24 (16,6%)	0.49
IgG -	2/21 (9,5%)	
IgM +	2/21 (9,5%)	0.64
IgM -	3/24 (12,5%)	
IgA +	2/24 (8,3%)	0.54
IgA -	1/21 (4,7%)	

Conclusions: The presence of CP in the coronary atherosclerotic plaques of patients with unstable angina did not identify a higher group of patients for presenting adverse events in the follow-up. A positive serological (IgG, IgM, IgA) result against CP was not related to a worse prognosis, either.

P2207 Cytomegalovirus expression in specimens from stable and unstable coronary lessions

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Background: Infection with human Cytomegalovirus (HCMV) has been reported in several epidemiological studies to play an important role in the pathogenesis of atherosclerosis. However, the frequency of HCMV detectable in atherosclerotic plaques and the possible effect on the pathogenesis of atherosclerosis remains to be established.
Materials and Methods: We examined 100 coronary atherosclerotic plaques derived from postmortem examinations, and 40 atherectomized specimens obtained via Directional Coronary Atherectomy (DCA) from coronary arteries from patients clinically diagnosed with either stable (n=62, 44,3%) or unstable angina (n=78, 55,7%). All specimens were analysed for the presence of HCMV DNA sequences using Polymerase Chain Reaction. Furthermore each specimen was stained with immunohistochemical methods using polyclonal and monoclonal antibodies for the presence of CD4+, CD8+ T-lymphocytes as well as for the detection of HCMV early antigen. Morphometrical analysis of each atherosclerotic plaque was performed using the digital image analysis software Lucia.
Results: HCMV was found to be present in 41 out of 140 specimens (29.28%) included in our study. HCMV infected cells expressed a diffuse nuclear or an apparent cytoplasmic staining corresponding to early or late stage of infection respectively. From these 41 specimens, 32 were derived from unstable coronary lesions (78.04%). This statistically significant difference was accompanied by a three-fold increase in CD4+ and CD8+ T-lymphocyte infiltration in HCMV-positive specimens compared with HCMV-negative ones.
Conclusions: In our study the presence of HCMV was considerably higher in unstable plaques and may be the trigger for activating T lymphocytes, which are proven to be one of the most important factors contributing to the progression of atherosclerotic plaques and to the development of unstable coronary lesions.

P2208 Are fungi involved in atherosclerosis?

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Objectives: There is growing evidence of a relationship between some infective agents (chlamydia pneumoniae and cytomegalovirus) and atherosclerotic process. We sought to determine a similar implication between fungi and atherosclerosis.
Methods: We studied atherosclerotic arterial fragments from 30 pts (24 M) undergoing peripheral vascular surgery (aorta, carotid, femoral and iliac arteries) and 30 fragments of non-atherosclerotic internal mammary arteries from pts undergoing bypass surgery (27 M). In the mean time, aortic valve fragments from 30 pts (16 M) undergoing valve replacement for aortic stenosis were analyzed. Each fragment was separated in 2 pieces: one for mycological analysis and the other for direct microscopic examination and culture on specific mediums. All fragments were manipulated with strict cautions in order to prevent any external contamination.
Result: Ten arterial fragment cultures (16.6%) showed fungal growth: 9 fragments originating from atherosclerotic lesions (9/30; 30%) and one from an internal mammary artery (1/30; 0.3%, $p<0.05$). Three fungal species were identified: Aspergillus, Cladosporium and Trichoderma. No correlation was found between the presence of fungi and atherosclerosis risk factors. None of the aortic valve fragments showed any fungal growth.
Conclusion: This study shows a significantly high affinity of some fungus species to atherosclerotic arterial intima but no affinity to pathological aotic valves or normal arteries. Further investigations are needed to clarify fungal involvement in atheroscerotic process.

P2209 Infectious pathogen burden and atherosclerosis: unstable atherosclerotic plaques contain T cells that respond to Epstein Barr Virus

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Background: T cell activation is an essential feature in the chain of events eventually leading to the development of acute coronary syndromes. Cytokines, especially interferon-gamma secreted by Th1 T cells are considered to have plaque destabilizing properties. However, at present it is not clear which antigens are responsible for this local activation of T lymphocytes. Several studies, including those from our laboratory have shown that the common infectious pathogen C.pneumoniae is able to activate T cells from human atherosclerotic lesions. Seroepidemiological studies however have suggested that also other pathogens may be involved. Therefore, we studied the possibility that Epstein Barr Virus (EBV), another common pathogen could be involved also in local intraplaque T cell activation
Methods: T cells were isolated from human carotid endartherectomy specimens (n=11) and T cell lines were generated. B lymphocytes from the same patients were transformed with EBV and cell lines generated. Proliferative responses of T cells using autologous EBV-B cells as antigen presenting cells (APC) were measured by ^{3}H-thymidine incorporation. A stimulation index (SI) > 3 was considered as a responding T cell line. The specificity was further analyzed by inhibiting antibodies against MHC class I and II antigens. In addition, the presence of EBV in atherosclerotic tissue (n=29) and normal vesselfragments (n=8) was analyzed by PCR.
Results: 4/11 patients showed a specific significant response against EBV (mean SI= 15.2). This response was usually both partly MHC class I and II restricted. PCR analysis showed EBV DNA in the plaques of 19/29 patients (66%). EBV DNA was never present in normal vessels (0/8 specimens)
Conclusions: These results suggest that besides C.pneumoniae also the common pathogen EBV may be involved in the local activation of T cells in atherosclerotic plaques, an observation which is in line with the current concept of the role of a "pathogen burden" in atherosclerotic disease.

P2210 Chlamydia pneumoniae induces monocyte migration through extracellular matrix via EMMPRIN and matrix metalloproteinase activation

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Proteolytic activity of matrix metalloproteinases (MMP) is thought to promote cell migration and the rupture of the atherosclerotic plaque. We have studied the effects of Chlamydia pneumoniae (C.pn.) on the initiation of matrix degrading activity in monocytes with special regard to the role of the "Extracellular MMP-Inducer" EMMPRIN. Infection of monocytic MonoMac6 cells or isolated monocytes with C. pn. for 48 hours significantly enhanced the mRNA and surface expression of the urokinase receptor (uPAR), membrane-type-1-MMP (MT1-MMP) and of EMMPRIN [quantitative RT-PCR, flow cytometry]. Antibody-crosslinking of EMMPRIN resulted in 2-fold baseline secretion of MMP-9 and enhanced C.pn.-induced MMP-9 secretion by 2-fold indicating a central role for EMMPRIN as a MMP inducer. C. pn. significantly enhanced the secretion of soluble uPAR and uPA as well as induced matrix degrading activity of the two gelatinases MMP-2 and MMP-9 [ELISA, SDS-PAGE-zymography]. Transmigration of C.pn.-infected monocytic cells through extracellular matrix components ("matrigel") was maximally enhanced (comparable with PMA-stimulation) and was inhibited by the MMP-inhibitor GM6001 (100%), recombinant TIMP-1 (51%) or TIMP-2 (50%), but not by the non-inhibiting control peptide for GM6001. Consistently, C. pn. stimulated monocytic cell migration through endothelial cell monolayers (HUVEC). The LPS-inhibitor polymyxin B abrogated LPS-induced matrigel invasion, but not C. pn.-induced cell invasion indicating, that endotoxin did not play a major functional role for C.pn.-induced cell invasion.
Conclusion: C.pn. induces monocytic matrix degradation and matrix invasion via activation of a proteolytic cascade involving the plasminogen and MMP activation system. This activation pathway seems to be independent of chlamydial LPS. These data indicate, that C.pn. may (1) promote monocyte recruitment into the atherosclerotic plaque and (2) contribute to the development of cardiovascular complications such as plaque rupture by the activation of matrix degradation.

P2211 Influenza infection exerts prominent inflammatory and thrombotic effects on the atherosclerotic plaques of apo E-deficient mice

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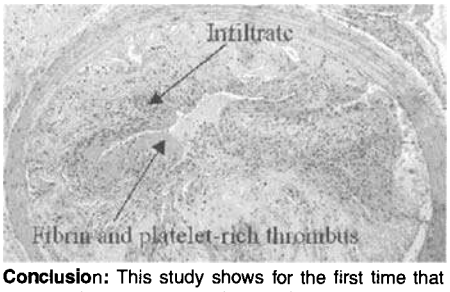
The role of infection in the development and complications of atherosclerosis has been the focus of much attention. We have previously reported that influenza vaccination was associated with reduced risk of recurrent myocardial infarction. Here, we report the effect of influenza A virus on the apo E -/- mouse, an animal model of atherosclerosis.

Methods: Twenty-four apo E -/- mice over 24 months old were injected with 1 LD50 (lethal dose 50) of influenza A virus intranasally. Ten wild-type C57BL/6 infected mice and 11 non-infected age-matched apo E -/- mice served as controls. Animals were sacrificed 3, 5 and 10 days after inoculation. Multiple aortic sections were studied histologically.

Results: The infected mice showed marked increase in intimal cellularity compared to the non-infected apo E -/- mice. No aortic abnormalities were seen in infected wild-type mice. Ten infected apo E -/- mice had a prominent subendothelial infiltrate composed of a heterogeneous group of cells that stained positively for smooth muscle cell actin, F4/80 (macrophages) and CD3(T lymphocytes). Infected animals with the focal cellular infiltrate had clusters of platelets in the lumen overlying the infiltrate. One case of subocclusive platelet aggregation and fibrin-rich thrombus was seen. Neither the subendothelial infiltrate nor the large platelet clusters and thrombus were seen in the non-infected mice.



Conclusion: This study shows for the first time that influenza infection promotes inflammation, growth, and thrombosis of atherosclerotic plaques. This may prove useful as a model for studying the roles of infection and inflammation in atherogenesis.

NEUROHUMORAL CONTROL MECHANISMS IN HEALTH AND DISEASE

P2212 Co-stimulation of different guanylyl-cyclase receptors in healthy men

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Differences in the effects of natriuretic peptides (NP) are still poorly understood. In particular, most of the known effects of both ANP and BNP are conducted by stimulation of the guanylyl-cyclase type A receptor. However in contrast to ANP, the effects of BNP are believed to be preserved in chronic heart failure. Recent findings in experimental studies support the presence of a BNP-specific receptor. We, therefore, investigated the haemodynamic effects of co-infusion of ANP, BNP, and as a control CNP, in addition to submaximal local dosage of ANP in the forearm vasculature of healthy subjects. Furthermore, in half of the subjects infusions were maintained for 5 times half-lives of the peptides to investigate if rapid desensitisation is present in humans.

Methods: In 11 healthy, male volunteers, arterial response to intra-arterial infusion of ANP (60pmol/100ml forearm volume/min) to cause submaximal NPR-A stimulation was measured. Then, co-infusion of either ANP, BNP or CNP in randomised order was administered to assess additional vascular response. After a washout period adjusted to the plasma half-live of the administered NP, ANP was restarted, followed by co-infusion of one of the NP not yet infused. After a further washout period, ANP was restarted, followed by co-infusion of the NP not yet co-infused. In 6 of the subjects, infusion time was adjusted to plasma half-lives of the peptides (5 times), and in 5, infusions were given for 5 minutes each.

Results: ANP alone caused the expected vasodilation from 2.7±0.3 to 6.0±0.9 ml/min/100ml forearm volume (FAV; $p<0.004$). This response remained unchanged in the group receiving short infusions (6.2±0.8 to 6.6±1.1 ml/min/100ml FAV), but was significantly reduced in the group receiving infusions over a longer period of time (6.5±1.2 to 4.5±0.7, $p<0.05$; response different between groups $p<0.05$). Co-infusions of ANP, BNP, and CNP caused a small additional vasodilation (mean 0.8±0.2 ml/100ml FAV/min, $p<0.01$). However, this additional vasodilation was identical in 3 groups, but blunted over time in the group receiving long infusions.

Conclusions: There seems to be rapid desensitisation of the guanylyl-cyclase type A receptor. Although our data do not support the presence of a BNP-specific receptor, the lack of additional response to stimulation of the type B receptor by CNP does not exclude it. Furthermore, the vasodilatory capacity through stimulation of guanylyl-cyclase receptors seems to be limited, irrespectively if one or more than one type of these receptors is stimulated.

P2213 ANP but not CNP modifies forearm vascular tone in CHF

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Background: Previous in vitro studies comparing the vascular effects of atrial natriuretic peptide (ANP) and c-type natriuretic peptide (CNP) in animal vessels indicated that arteries are the major site of action for ANP whilst CNP acts mainly on veins. We recently demonstrated that ANP causes marked forearm venodilation in healthy controls. In this study we compared the effects of ANP and CNP on forearm blood flow (FBF) and venous capacitance in subjects with chronic heart failure (CHF).

Methods: We infused incremental doses (0.05μg/min, 0.5μg/min, 1μg/min) of ANP (n=13) or CNP (n=7) into the brachial artery of 20 subjects with CHF (NYHAII/III). Changes in baseline forearm venous volume, compliance and tone were assessed in all patients using radionuclide plethysmography. In brief; Following radiolabelling of red cells, venous pressure/volume relations (PVR) were constructed by obstructing venous outflow in a stepwise manner for 1 minute. During each 1-minute interval a dynamic picture of the forearm was recorded using a gamma camera. Vascular volume was plotted against occluding cuff pressure. Forearm blood flow was measured in 11 subjects (ANP; n=5/CNP; n=6) using strain gauge plethysmography. Natriuretic peptide (NP) (20 subjects) levels and cGMP (15 subjects) production were measured by radio-immuno assay.

Results: (mean±SEM). NP levels in the venous effluent of the infused arm increased from 95±17pg/ml to 251±40pg/ml (ANP 1μg/min) and from 10±1pg/ml to 1253±49pg/ml (CNP 1μg/min); $P<0.01$ for both. ANP infusion caused a modest increase in FBF from 2.6±0.3ml/100ml forearm volume (fv) to 3.9±0.9ml/100ml fv; P=0.1. This was associated with an increase in cGMP from 7.2±1.3pg/ml to 25±5.6pg/ml.; P=0.01). CNP infusion did not change FBF; 2.6±0.4ml/100ml fv to 2.9±0.2ml/100ml fv; P=NS, despite a modest increase in cGMP from 10.3±1pg/ml to 15.4±4pg/ml; P=0.2. However, whilst ANP infusion caused a dose-dependent parallel upward shift of the PVR (reflecting venodilation) associated with an increase in forearm venous volume (2%; P=0.2, 5%; $P<0.01$ and 14%; $P<0.001$), CNP had no significant effects on forearm venous volume (-2%, 1%,7%, P=NS for all).

Conclusion: ANP but not CNP modifies venous capacitance in CHF.

P2214 The angiotensin II response to an acute exercise stimulus and the angiotensin converting enzyme genotype

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Background: The angiotensin converting enzyme (ACE) insertion/deletion (I/D) polymorphism is associated with resting ACE activity such that DD>ID>II. The D allele is strongly associated with increased exercise-induced left ventricular hypertrophy (LVH) and cardiovascular risk. We therefore examined the relation between ACE genotype, exercise, circulating ACE and Angiotensin II.
Methods: Seventeen (9DD, 8II) healthy, male (22.9±1.9 years, 178.6±2.8 cm, 71.9±2.2kg) participants who performed 20 minutes of exercise on a fixed ergometer at 70% of Vo2 max. Venous samples were taken at rest, immediately after exercise and 40 minutes post-exercise and plasma extracted. ACE assays were analyzed by a fluorometric method using Z-Phe-His-Leu as substrate. Angiotensin II samples were drawn into chilled tubes containing a renin inhibitor with plasma and shock frozen in liquid nitrogen. Paired t-tests examined the whole-group change in ACE and Angiotensin II with ANOVA for genotype differences. All figures: mean±sem, ACE activity (nmol His/Leu/ml/min), Angiotensin II (pg/ml plasma).
Results: Baseline ACE activity was significantly different ($p<0.001$) between the II (24.9±1.8), and DD subjects (45.5±2). The whole-group increase in ACE activity with exercise (5.7±0.7) was significant ($p<0.001$), with the difference in ACE between II (29.9±2.1 and 27.2±2.1) and DD (51.8±3 and 48.6±2.3) subjects persisting ($p<0.001$) for both immediate and 40mins post-exercise. Baseline Angiotensin II was no different between genotypes (2.8±1.2 and 2.6±1.5, DD and II respectively, p=0.9). Angiotensin II levels rose significantly (27.6±2.7, $p<0.001$), but were no different between genotypes immediately post-exercise (25.6±2.9 and 33.9± 5.3 for DD and II subjects, p=0.2). However, there was a significant difference 40 minutes after exercise (increased 19.2±4.6, and 6.2±1.6 for DD and II respectively, p=0.03).
Conclusions: This is the first report that DD subjects demonstrate a greater rise in Angiotensin II at 40min post-exercise than II subjects. This may reflect increased levels of circulating ACE persisting after exercise. The hypertrophic and vasoconstricting action of Angiotensin II may thus facilitate the increased LVH in DD subjects with exercise.

P2215 Norepinephrine release is reduced in cardiac tissue of diabetic patients

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Background: Cardiac sympathetic nerve activity has substantial pathophysiologic and prognostic implications in heart diseases. We therefore sought to relate patient characteristics to norepinephrine release in specimens of atrial tissue obtained during bypass surgery.
Methods: Norepinephrine release was determined in incubated human atrial tissue under baseline conditions as well as during electrical field stimulation (5 min, 5 V, 4 Hz) and was measured by high performance liquid chromatography with electrochemical detection.
Results: Stimulation-induced norepinephrine release was reduced by approximately 25% in atrial tissue from diabetics (n = 19) as compared to nondiabetics (n = 43) (46 ± 5 vs. 62 ± 4 pmol/g; $p < 0.05$), whereas baseline release did not differ (14 ± 2 vs. 17 ± 2 pmol/g). Conversely, neither baseline nor stimulation-induced norepinephrine release was altered in patients with arterial hypertension (n = 40) compared to those without respective attribute (n = 22) (baseline norepinephrine 16 ± 2 vs. 17 ± 2 pmol/g and stimulation-induced norepinephrine 54 ± 4 vs. 62 ± 5 pmol/g). Analysis of cardiac function and norepinephrine release in 56 patients revealed a positive correlation of baseline release and preoperative left ventricular ejection fraction ($r = 0.32$, $p < 0.05$), while stimulation-induced release was not correlated with ejection fraction ($r = 0.22$). Finally, no correlation was found between age and cardiac norepinephrine release (baseline and stimulation-induced norepinephrine release each $r = 0.02$, $n = 62$).
Conclusions: In atrial tissue of diabetic patients stimulation-induced norepinephrine release from sympathetic nerve endings is reduced and this may contribute to sympathetic neuropathy. Furthermore, patients with impaired cardiac function had reduced norepinephrine release probably due to depletion of transmitter stores. Other characteristics such as age or arterial hypertension were not related to altered norepinephrine release.

P2216 Enhanced vasoconstriction in chronic heart failure: a potential consequence of increased ET-1 and failed natriuretic peptide counter-regulation

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Background: Peripheral vasoconstriction is increased during exercise as is neurohumoral actovation as part of compensatory and counter-regulatory mechanisms in patients with chronic heart failure (CHF).
Objectives: To assess brachial artery (BA) reactivity in association with plasma levels of endothelin-1 (ET-1) and cardiac natriuretic peptides - atrial (ANP) and brain (BNP)natriuretic peptide, in response to graded increment in exercise intensity to determine the balance between major compensatory mechanisms.
Methods: Fifteen-men aged 56.7±8 (Mean±SD)years with NYHA class I-IV CHF and LV ejection fraction < 35% (radionuclide),cardiac index 1.5±0.22 L/M^2/min, mean pulmonary capillary wedge pressure 21.0±9.3mm Hg were studied. Using high-resolution (3-11MHz linear array transducer)ultrasound (SONOS 5500, Hewlette Packard, USA)technique with a resolution capability of 0.1mm, we measured BA diameter at rest and within 90 seconds after leg exercise (arm held non-active) to determine BA reactivity in response to submaximal (SME)and maximal (ME) exercise. Cardiopulmonary exercise testing was performed to determine peak O2 consumption (VO2)using breath-by-breath gas analysis (AMIS 2000, Denmark). SME was defined as 80% of the subjects's ME capacity as measured by recent exercise testing prior to study. ME was terminated after the subject has reached a state of exhaustion, which was performed after an interval of 60-90min to allow recovery from SME. Venous blood samples were obtained at baseline and peak SME and ME testing for the measurement of lactate, ET-1 (Biotrak ET-1 ELISA System, Amersham, England)ANP and BNP(immunometric assay,Shionara, France).
Results: VO2 increased from 18.1±5.5 to 22.3±7.3 ml/kg/min(P=0.002) and blood lactate from 1.88±0.36 to 2.5±0.58mmol/L($P<0.0001$) with increment from SME to ME. BA showed a graded decrease in its diameter, inferred as an increase in constriction (calculated as % change in diameter from baseline)from 6.1±4.7% to 7.2±4.6% (P=0.004)with increment in exercise intensity. Plasma levels of ET-1 (2.06±0.60 to 2.5±0.61pmol/L;P=0.0001)showed a similar increment but ANP (47.1±37.8 to 38.4±28.4pmol/L;P=0.16)and BNP (28.4±24.1 to 31.3±27.3pmol/L;P=0.15)levels demonstrated initial increase with no further rise with increase in exercise intensity.
Conclusion: Incremental BA constriction and plasma ET-1 levels with graded increase in exercise suggest an exaggerated vasoconstrictor state in CHF. Lack of appropraite rise in plasma levels of ANP and BNP indicate an insufficient counter-regulation.

CONGENITAL HEART DISEASE, RIGHT HEART AND MISCELLANEOUS

P2217 Aberrant tendinous chords with tethering of tricuspid leaflets: an unknown congenital anomaly causing severe tricuspid regurgitation in adults

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Background: We describe a novel mechanism of tricuspid regurgitation in adults due to tethering of the tricuspid valve leaflets by aberrant tendinous chords.
Methods: The last 13'500 consecutive echocardiographic studies from our facility were reviewed to identify patients with severe tricuspid regurgitation. Tethering was defined as aberrant tendinous chords to one or more tricuspid valve leaflets resulting in incomplete coaptation and tricuspid regurgitation.
Results: Ten patients (5 male and 5 female, mean age = 38 years, range = 12 - 73 years) with aberrant tendinous chords tethering one or more tricuspid valve leaflets were identified. One or more of each of the tricuspid valve leaflets were found to be affected. Tethering was the only mechanism of tricuspid regurgitation in three patients, whereas it was associated with short primary tendinous chords (i.e. with normal insertion at the leaflet tip) in seven patients. Six patients had associated congenital heart disease (atrial septal defect, congenitally corrected l-transposition of the great arteries, d-transposition of the great arteries, situs inversus with congenitally corrected d-transposition of the great arteries and two patients with pulmonary stenosis).
Conclusions: Tethering of the tricuspid valve leaflets due to aberrant tendinous chords is a distinct and previously unrecognised cause of tricuspid regurgitation in adults. This anomaly is frequently associated with short non-aberrant tendinous chords. Awareness of this mechanism of tricuspid regurgitation is of high clinical relevance and must be taken into consideration during reconstructive surgery of the tricuspid valve.

P2218 Unicuspid, bicuspid and quadricuspid aortic valves diagnosed by transoesophageal echocardiography

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Background: The bicuspid aortic valve (BAV) is the most frequent congenital malformation of the heart, whereas unicuspid (UAV) and quadricuspid aortic valves (QAV) are very rare. Incidence and associated lesions in patients undergoing TEE have not been well described.
Methods and Results: Over a 10-year period, 4827 adult patients were studied by TEE and prior TTE. QAV was present in 3 patients (0.06%). 1 patient (age 32) with associated ventricular septal defect had 4 equal valve cusps and showed normal QAV function. The second patient (age 59) with associated fibromuscular subaortic stenosis had 1 small and 3 large cusps with grade IV aortic regurgitation. A third patient (age 46) with isolated QAV had 4 unequal cusps with grade II aortic regurgitation. No QAV had evidence of stenosis or endocarditis. BAV was diagnosed in 38 patients (0.8%, 8f, 30m, mean age 48 y) and was regurgitant (n=17), stenotic (n=2), both stenotic and regurgitant (n=12) or showed normal BAV function (n=7). Associated lesions were: aortic valve (n=5) or mitral valve prolapse (n=1), aortic aneurysm/ dissection (n=3), mitral valve aneurysm (n=5), and subvalvular aortic stenosis, sinus of Valsalva aneurysm, aortic coarctation or aortic arch atresia (1 patient each). Infective endocarditis was present in 11 patients (active n=9, remote n=2, only BAV n=5, BAV and/ or mitral valve n=6). Diagnosis of UAV was made in 1 patient (age 45) with pure aortic regurgitation of grade IV caused by high leaflet redundancy with leaflet prolapse and associated endocarditis. There was no stenosis in this unicommissural valve. 1 UAV, 1 QAV and 19 BAV patients underwent aortic valve replacement with surgical confirmation of the valve morphology and associated lesions. The incidence of congenitally abnormal valves in TEE patients compares well with the figures reported in the literature for autopsy series.
Conclusion: QAV is rare, in case of unequal cusps regurgitant, and occurs alone or in association with other congenital abnormalities. BAV is found more frequently, may be stenotic and/or regurgitant and is prone to infective endocarditis. Associated lesions in BAV patients may be congenital but frequently are acquired. UAV is extremely rare and may present in adults with pure aortic regurgitation without stenosis.

P2219 Preparticipation cardiovascular athletic screening examination using echocardiography in 6610 children and adolescents: a 12 years' experience

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Background: Preparticipation Cardiovascular Screening Examination (P.C.S.E.) is considered mandatory for the safe training of young athletes for the prevention of sudden death as well for the early diagnosis of cardiac abnormalities that require limited athletes' participation, medical or interventional treatment, follow-up and chemoprophylaxis. During the last 12 years we examined an exceptionally high number of children and adolescents for P.C.S.E. The aim of the study was to estimate the incidence and the type of cardiac abnormalities in young athletes and to evaluate the contribution of the echocardiography to that purpose.
Methods: We examined 6610 children and adolescents (5-19 yrs, mean 11) without known cardiac disease. A detailed medical history, physical examination, electrocardiogram and an echocardiogram were performed from the same physician.
Results: Two hundred and thirty participants (3.5%) demonstrated cardiac abnormalities: 70 (1.1%) aortic valve diseases (bileaflet AV, regurgitation, stenosis), 57 (0.6%) shunts (ASD, VSD, PDA), 82 (1.2%) mitral valve prolapse, 12 (0.2%) pulmonary valve stenosis, 5 (0.08%) WPW, 1 hypertrophic cardiomyopathy, 1 dilated cardiomyopathy, 1 coarctation of the aorta and 1 primary pulmonary hypertension.
Conclusion: 1) A significant number of children and adolescents demonstrate major cardiac abnormalities statistically considerably greater than the one that it is referred to incidents of congenital heart disease during birth. 2) Low incidents of hypertrophic cardiomyopathy (major cause of sudden death during training) and of mitral valve prolapse highlights the fact that the echocardiographic findings of these abnormalities appear progressively until adulthood and the non discovery during childhood or adolescence does not exclude them. 3) echocardiography contributes to its maximum in diagnosis of cardiac abnormalities in athletes under the precondition that a detailed medical history and a careful interpretation of ECG precedes and special care is taken to avoid false positive results of the test which are the major problem of the overusage of the method.

P2220 Effects of different training protocols on right ventricular myocardial function in competitive athletes: a tissue Doppler study

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Hemodynamic overload due to long-term physical training involves both left (LV) and right (RV) ventricular chamber, inducing changes in cardiac structure globally described as "athletes heart". Although standard Doppler echocardiography has been widely used to distinct athlete's heart from pathologic LV hypertrophy, few reports have described the RV myocardial adaptation to extensive physical exercise. Aim of the study was therefore to analyze the different involvement of RV myocardial function in LV hypertrophy induced by either endurance or strength training in top level athletes.
Methods: Standard Doppler echo and pulsed Tissue Doppler (TD) of mitral and tricuspid annulus were performed in 36 competitive endurance athletes (long-distance swimmers) (ATE) and in 28 strength-trained athletes (short-distance swimmers) (ATS). By use of TD, the following parameters of myocardial function were assessed: systolic peak velocities (Sm), pre-contraction time, contraction time, early (Em) and late (Am) diastolic velocities, Em/Am ratio, relaxation time.
Results: the two groups were comparable for age and sex, but ATS at rest showed higher heart rate, systolic blood pressure, and body surface area. LV mass index and fractional shortening did not significantly differ between the 2 groups. However, ATS showed increased sum of wall thickness (septum + posterior wall) ($p<0.001$) and relative wall thickness, while LV stroke volume and both LV and RV end-diastolic diameters ($p<0.001$) were greater in ATE. All transmitral and transtricuspid Doppler indexes were higher in ATE, with increased E/A ratios. TD analysis showed in ATE higher Sm, Em and Em/Am ratio as well as longer relaxation time both at mitral and at tricuspid annulus level. Distinct multiple linear regression models evidenced independent positive association between RV peak Em velocity and LV end-diastolic diameter (beta: 0.75; $p < 0.0001$) in ATE, and independent direct correlation of RV peak Sm velocity with sum of wall thickness (beta: 0.62; $p < 0.001$) and LV end-systolic stress in ATS. Conclusions: Early diastolic RV myocardial function is positively influenced by preload increase in ATE, while increased afterload and LV wall thickness seem to induce mainly an enhancement of regional RV systolic function in ATS.

P2221 Assessment of systolic right ventricular function by Doppler tissue imaging of the tricuspid annulus

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Background: Peak systolic velocity obtained by Doppler Tissue Imaging (DTI) of the mitral annulus has been shown to correlate with systolic left ventricular function. The intention of our study was to assess whether such a relation exists between the peak systolic velocity of the tricuspid annulus and systolic right ventricular function.
Method: We examinded 225 patients (pts) divided in three groups (group 1: 95 pts without cardiovascular disease; group 2: 59 pts with impaired right ventricular function: group 3 71 pts with impaired left ventricular function or pulmonary hypertension but normal right ventricular function) by transthoracic echocardiography. The mean value of three methods to determine right ventricular ejection fraction (monoplane Simpson's method; biplane pyramidal approximation; monoplane ellipsoid approximation) was used as reference for systolic right ventricular function (RVEF). Tricuspid annular velocities were recorded by pulsed wave DTI at the lateral tricuspid annulus.
Results: RVEF was significantly lower in group 2 (38±14%) in comparison to group 1 (67±6%) and 3 (67±6%) as expected from the inclusion criteria. Left ventricular ejection fraction values in group 2 (46±17%) and group 3 (53±15%) were less than in the control group 1 (68±4%; $p<0.001$). Peak systolic velocity at the lateral tricuspid annulus (TVLAT) differed in the three groups. TVLAT was significantly lower in group 2 than in group 1 and 3 (9.8±2.4 cm/s vs. 15.6±2.5 cm/s and 14.6±3.9 cm/s; $p<0.001$). Linear regression analysis showed a correlation between TVLAT and RVEF ($R=0.57$; $p<0.0001$). A cut-off value of TVLAT <12.5 cm/s has a sensitivity of 85%, a specifity of 80% and a positive predictive value of 58% to detect an RVEF<55%. The negative predictive value of the test (TVLAT <12.5cm/s) is 94%.
Conclusion: Diminished peak systolic velocity of the lateral tricuspid annulus obtained by pulsed wave DTI can be used as a marker for impaired systolic right ventricular function possibly regardless of systolic left ventricular function. A peak systolic velocity of the lateral tricuspid annulus of >12.5cm/s accurately predicts normal right ventricular function.

P2222 Clinical studies of right ventricular wall motion by pulse-wave Doppler tissue imaging in patients with coronary artery disease

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Objectives: The right ventricular (RV) wall motion by pulse-wave Doppler tissue imaging (PW-DTI) in patients with coronary artery disease has not yet been well investigated. The aim of this study was to evaluate RV wall motion qualitatively and quantitatively by PW-DTI, and its clinical significance. Methods: The study population included 32 consecutive patients who underwent coronary angiography. Based on the conronary lesions, patients were devided into three groups. Group A consisted of 11 patients with normal coronary arteries. Group B included 15 patients with right coronary narrowing. Group C comprised 6 patients with normal right coronary arteries and stenotic left coronary arteries. Volume sampling of PW-DTI was placed at the basal, middle and apical segment of the RV free wall in the apical 4-chamber view.The peak systolic velocity (Vs), the systolic velocity integral (VTI-S), the early peak diastolic velocity (Ve), the late peak diastolic velocity (Va), the the onset of early diastolic wave (Q-E), the time interval from the onset of QRS wave of the ECG to the peak diastolic velocity (Q-E)was determined. Results: (1) In the middle segment of the RV free wall, Q-E and Q-Ep in Group B were significantly longer than those in Group A (p=0.001, p=0.049 respectively). In the apical segment of the RV wall, Q-E in Group B was significantly longer than that in Group A as well (p=0.048). (2) In the basal segment of the RV wall, Q-E in Group C was significantly longer than that in Group A (p=0.02). In the middle segment of the RV free wall, Q-E and Q-Ep in Group C were significantly longer than those in Group A (p=0.01, p=0.04 respectively). (3) In the middle segment of the RV wall, S-VTI in Group B was significantly lower than that in Group C (p=0.018). In the apical segment of the RV wall, Vs in Group B was significantly lower than that in Group C (p=0.03). (4) No significant difference of Ve and Va were found in each segment among all groups (all $p>0.05$). Conclusions: Our findings demonstrate that the prolongation of Q-E and Q-Ep in the middle segment of the RV free wall indicates coronary narrowing, and the decrease of S-VTI in the middle segment of the RV free wall or the lowering of Vs in the apical segment of the RV free wall indicates right coronary stenosis. PW-DTI is a new noninvasive method to detect coronary artery disease.

P2223 Evidence for significant ischaemic right ventricular dysfunction during dobutamine stress echocardiography

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Background: In clinical practice the concern is always focused on the effect of coronary artery disease on the left ventricle, even during stress.
Aim: To assess right ventricular (RV) behaviour in addition to that of the left ventricle during stress echocardiography in order to identify markers of dysfunction that may contribute to the patient symptoms.
Subjects: We studied 33 patients (mean age 58±5 years, 30 males) with triple vessel coronary artery disease using the conventional dobutamine stress Echocardiography protocol starting with 5μg/kg/min with similar incremental doses every 3 minutes for up to eight stages. RV function was assessed from M-mode recording of the free wall amplitude of motion and spectral Tissue Doppler (TD) for its systolic and diastolic velocities. RV filling velocities were also measured from the pulsed wave Doppler recordings. The findings were compared with those from 15 control subjects (mean age 58±11 years).
Results: At rest- Right ventricular size was normal, inlet diameter <3.5 cm, and free wall amplitude, shortening and lengthening velocities not different from controls. RV filling velocities were slightly reduced in patients but E/A ratio was maintained.
At peak stress: RV free wall amplitude failed to increase compared to controls (2.3±0.6 vs 3.0±0.5 cm, $p<0.001$. The peak TD systolic velocity increased as in controls suggesting maintained RV inotropic function. In contrast to normal behaviour, early TD diastolic velocity failed to increase (11.0±4.0 vs 14±3.5 cm/s, $p<0.001$) and 8/33 patients developed significant post ejection shortening ($P<0.001$). This contributed to the fall in RV E/A ratio from 1.1±0.3 to 0.76±0.4, $p<0.001$.
Conclusion: In patients with multivessel coronary artery disease, the right ventricular free wall may demonstrates ischaemic disturbances, similar to those seen on the left side with stress. This may contribute to patient's symptoms and exercise intolerance known in coronary artery disease.

P2224 Anatomical changes of right heart after percutaneous atrial septal defect closure with Amplatzer device

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Background: Percutaneous atrial septal defect (ASD) closure with Amplatzer septal occluder (ASO) device is a safe and effective technique in reducing left to right shunt. However, the response of the adult's right heart after device closure is incompletely understood. The aim of this study is to evaluate the right heart response to ASD device closure in an adult population at 6 months.
Methods and Results: Between May 1999 and September 2001, 36 adult patients (21 female) with a mean age of 44.6+15.1 years (range 26 to 84) had a percutaneous ASD closure with ASO-device. A trans-thoracic (TTE) echocardiography evaluation was done at 24 hours and at 6 months after procedure. Right ventricle outflow diameter (RVOTD), right ventricle inlet diameter (RVID), right atrium width (RAW) and right atrium length (RAL) were measured
The mean ASD diameter was 14.4+7.2 mm and mean ASO-device size was 19.8+ 8.2 mm. ASO-device was implanted successfully in 94.4% (34/36) of patients. A residual shunt of 3 mm was shown in only one patient. The TTE was performed in all patients in whom ASO device was deployed successfully. Mean RAL and mean RVOTD reached significant reduction at six months compared with TTE post-procedural measurements (53.1+6.5 vs 48.5+ 5.2 mm, $p<0.005$ and 41.2+ 6.7 vs 35+5.1mm, $p<0.005$ respectively). Mean RVID size showed a trend toward shortening without reaching significance at six months (44.2+ 4.3 vs 42.6+4.5 mm, p: 0.056). Mean RAW did not change significantly (46.4+4.5 vs 44.9+ 5.1 mm, p: 0.08).
Conclusions: After percutaneous ASD closure device RAL and RVOTD had a significant reduction at six month. However, morphology of the right heart did not return completely to normal suggesting an impaired ability of the right heart to remodel after prolonged volume overload in these older patients.

P2225 Acute changes in right ventricular wall deformation after transcatheter atrial septal defect closure. An ultrasound strain and strain rate study

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Background: The assessment of right ventricular (RV) function by conventional echocardiography is still not satisfactory. Strain and strain rate imaging are the new techniques for quantitation of regional myocardial function for both left and right ventricles.
Purpose: To verify a hypothesis that strain and strain rate indices can identify the local changes in wall deformation due to the acute volume unloading of the right ventricle.
Methods: 15 consecutive pts with ASD t.II (defect size:1.3± 0.6cm),aged 7-68 years(33±22;7M,8F) referred for transcatheter septal closure were scanned within 24 h hours before and after closure procedure using conventional Mmode (RVDD/RVDS) and Doppler (Ao VTI, Pulm VTI) imaging. Additionally high frame rate Colour Tissue Velocity data were acquired in apical 4ch view and analyzed off-line (Speqle®)to derive longitudinal systolic strain rate (SR sys), maximal strain (S max) and systolic velocity (V sys)for the RV free wall, septum and LV lateral wall. T paired test was used to compare the measurements before and after closure.
Results: The mean heart rate was 81±18 before procedure and 78±16 after closure (p=ns). Within 24 h after procedure we observed significant reduction in RV diameter (RVDS:2.6±0.5 vs 2.3±0.2 cm, p=0.02; RVDD:3.0±0.6 vs 2.5±0.2cm, p=0.01) and pulmonary flow (PulmVTI: 22.0±8.0 vs 15.7±2.8, p=0.03. Longitudinal S max measured at medial part of the Rv wall decreased significantly (36±10% vs 28±9%, p=0.001), however SR sys and Vsys remained stable (2.0±0.4 1/s vs 2.0±0.7 1/s, ns and 9.0±2.6 cm/s vs 9.8±2.3 cm/s, ns respectively). After the closure of septal defect regional function among septal and LV lateral segments remained unchanged.
Conclusions: Strain and strain imaging is a feasible method to quantitate longitudinal RV wall regional function. In this clinical model of acute RV volume reduction strain measurements reflect the changes in deformation induced by volume unloading of the RV. Strain rate indices are less volume dependent and may better characterize contractile conditions of the right ventricular myocardium.

P2226 Intracardiac and intraluminal echocardiography: standard approaches and clinical benefit

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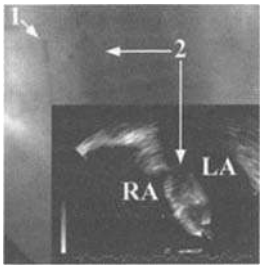
Background: In some clinical scenarios, transoesophageal echocardiography (TEE) have limitations. This study sought to test whether intracardiac and intraluminal echocardiography (ICLE) including two-dimensional, M-mode, and Doppler analysis with a miniaturised, multiple-frequency transducer tipped catheter is suitable to guide catheter interventions.

Method: ICLE was employed in 10 animals using 6 standard approaches. In 12 patients undergoing device closure of patent foramina ovalia (PFO) (n = 6) or atrial septal defects (ASD) (n = 3), or aortic stent implantation in DeBakey type III dissection (n = 3), interventional procedures were guided by ICLE and, for comparison, also by TEE.

Results: Standard approaches to the atria and the abdominal aorta are introduced: 1 – transvenous imaging of the abdominal aorta; 2 - transatrial imaging of the interatrial septum, the atria, the pulmonary veins, and the ventricles. ICLE was found to be helpful for guiding specific interventional procedures, especially device closure of atrial septal defects and patent foramina ovalia. In comparison with the conventional TEE-guidance, the technique reduces fluoroscopy time: 6.5 min. vs. 8.9 min., $p < 0.0011$. In contrast to the examinations by use of TEE, neither general anesthesia nor sedation was required using ICLE. After aortic stent implantation, flow in the false lumen of the abdominal aorta was demonstrated being brought to a standstill. ICLE also helps to effectively protect side branches originating close to the stent. Complications did not occur.



1 - ultrasound cath., 2 - closure-device.

Conclusions: ICLE adds to conventional TEE and promises to become a clinical alternative for guiding interventional procedures. With the patient in a supine position, ICLE is better tolerated than TEE.

P2227 Potential value of intracardiac echocardiography during invasive electrophysiologic procedures

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Background and aim of the study: Interventional electrophysiology often requires accurate identification of cardiac anatomical structures in order to improve radiofrequency catheter ablation (RFCA) results. Aim of our study was to test the usefulness of intracardiac echocardiography (ICE) to guide RFCA procedures.

Populations and methods: We selected 10 patients (6 males; mean age 64+8 years) with frequent episodes of paroxysmal atrial fibrillation or flutter (7 pts) or left sided accessory pathways (3 pts) candidate to RFCA procedures. ICE was performed via left femoral or right internal jugular vein with a 9F-9MHz mechanical echo catheter with a rotating ultrasound trasducer (Ultra-ICE Boston Scientific).

Results: ICE was feasible in all patients without complications. Echocardiographic images were evaluated on-line by an experienced cardiologist and presented to the electrophysiologist in order to properly guide the interventional procedure. ICE allowed identification and location of the following anatomical structures: venae cavae orifices, right atrial appendage, crista terminalis, fossa ovalis, Koch triangle, tricuspid annulus. In particular, in patients submitted to atrial flutter and/or fibrillation ablation procedures, continuity of the cavotricuspidal isthmus and the intercaval lesions was confirmed. One of the major advantages of ICE was the possibility to monitor and guide transeptal puncture and to identify pulmonary veins orifices in order to allow a precise mapping of atrial fibrillation triggering foci. Finally, proper electrocatheter adherence to the endocardium before ablation and formation of microbubble or coagulum and pericardial effusion during ablation were easily verified. ICE guided RFCA procedures resulted in a reduced radiations exposure time for both patient and operator (13±6 min vs 21±7 min, $p<0,05$, when compared to a similar matched group of patients who underwent only fluoroscopy guided procedures).

Conclusions: ICE during interventional electrophysiologic studies is feasible and safe. It allows a comprehensive visualization of cardiac structures that can not be precisely identified by fluoroscopy. ICE guided RFCA represents a promising technique that makes interventional procedures potentially safer and more effective.

P2228 Usefulness of a personal ultrasound Imager at the outpatient cardiology clinic

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Background: Recently, small personal ultrasound imagers (PUI) with excellent imaging performance became available. These devices can be integrated in the physical cardiovascular examination.

Aim: To determine the diagnostic performance and cost-effectiveness of a new PUI (OptiGoTM, Philips Medical Systems) at the cardiology outpatient clinic, using a standard high-end ultrasound system (SE) as a reference.

Methods: 213 new patients (mean age 53 ± 17, 167 male) referred to the cardiology outpatient clinic were enrolled in the study. All patients underwent an examination with the PUI and subsequently a complete echocardiographic study with a SE by a second investigator blinded to the results of the other. The diagnosis of the PUI was compared to the clinical diagnosis/question of the referring physician. Cardiovascular findings were divided into abnormalities of major and minor significance. Major findings were considered those who led to further diagnostic evaluation or alter the prognosis or the therapeutic management of the patient. Unsuspected significant findings were noted and all PUI data were compared with those obtained with the SE.

Results: The PUI was able to answer/confirm the requested clinical question/diagnosis in 198/213 (93%) patients. In the remaining 7% of the patients a SE examination did not add any further information and a transoesophageal study was regarded as necessary for the evaluation of cardiac source of embolism. A further hemodynamic assessment with the Doppler feature was regarded as useful in 29 (13,6%) patients. The agreement between the two devices for the detection of major abnormalities was 97%, kappa=0,92. The PUI missed major abnormalities in 4 (1,8%) patients. 7 out of 57 patients (12,2%) diagnosed normal with the PUI showed minor abnormalities with the SE. 75 of 124 (60%) major abnormal findings detected with the PUI were additional and unsuspected findings. The negative predictive value of the PUI in identifying patients with significant abnormalities was 98% and the positive predictive value 96%. As the clinical question could be answered with the use of the PUI in 93% of the patients, a further echo analysis with the SE could have been avoided in 75,6% of patients.

Conclusion: Echocardiographic assessment of new patients with a PUI at the outpatient clinic of the cardiology department can lead to instant diagnosis and to detection of unsuspected significant findings. This can lead to an improvement of the health care service in terms of better patient's care and of cost savings.

P2229 Comparison between echocardiographic studies made with new portable devices and conventional echocardiographic studies

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Background and objectives: New miniaturized echocardiographic devices are actually available. Previous studies show an improvement in the detection of important cardiovascular pathology compared with physical examination, however, its diagnostic accuracy in comparison with the results obtained using a high level echocardiographic platform is still not kwnown. The purpose of this study is to compare the result of examinations made with these devices, and the results obtained in the echocardiography laboratory, in order to add evidence to similar recent studies.

Methods: Two hundred and eleven consecutives unselected patients were imaged by cardiologists with experience in echocardiography (level III training) and then compared with the standard examination performed at echocardiographic laboratory with an upper platform and interpreted by an experienced echocardiographer.

Statistical analysis

	HD	Standard	p
Pericardial Effusion	6.16%	6.64%	0.656
LV enlargement	16%	17%	0.638
LA enlargement	50%	60%	0.003
LV hypertrophy	24%	35%	0.000
RV enlargement	5.6%	8.5%	0.134
Aortic root enlargement	0.94%	4.7%	0.011
regional motion abnormalities	3.6%	3.89%	0.587
Aortic regurgitation	28%	32%	0.207
Mitral regurgitation	53%	63%	0.05
Tricuspid regurgitation	41%	49%	0.015

The number of diagnoses with the handheld device (HD) and standard study are shown and also the statistical significance.

Results: We did not found statistical differences estimating the global and regional left ventricular systolic function, the presence of pericardial effusion and ventricular chamber enlargement. The device however failed detecting left ventricular hypertrophy, left atrial enlargement and the presence and severity of regurgitation, underestimating its degree. **Conclusions:** Although its limitations due to the characteristics of the device, when used by cardiologists trained in echocardiography it can be useful, providing important information, however a significative number of diagnoses are missed.

P2230 Significance of leucocyte count changes during stress echocardiography

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The aim of this study was to assess whether positive exercise stress echocardiography (ESE) uncovered presence of acute inflammation and whether transient, stress induced myocardial ischemia (m.i.) accelerated inflamatory process.

Methods: In the study group of 48 patients (32 male and 16 female; mean age 59.3 ± 5.3 years) with known or suspected coronary artery disease submaximal or symptom limited bicycle ESE was performed. ESE identified ischemia by the occurrence of wall motion abnormality (WMA) with stress - positive ESE. In all patients before and after ESE wall motion score (WMS) was calculated. At baseline and after ESE, in all pts total and differential white blood cell count (WBCC) were measured.

Results: During ESE 28 (58.3%) patients had new, transient WMA, while 20 (41.7%) pts were without ischemia. Baseline values of total WBCC and neutrophil count were significantly higher in patients with positive compared to those with negative ESE ($P<0.05$ and $P<0.05$). After ESE in patients with stress induced WMA value of total WBCC increased significantly (from 7.8 ± 2.6 to 9.2 ± 2.3 x 109/L, $P<0.05$) as well as the value of neutrophil count ($P<0.05$). In patients without stress induced WMA, during ESE total WBCC slightly changed (from 6.3 ± 1.9 to 5.9 ± 2.1 x 109/L, NS) as well as neutrophil count (NS). After ESE the difference in total WBCC and neutrophil count between patients with positive and patients with negative ESE become more pronounced ($P<0.001$ and $P<0.001$). In patients with positive ESE and increased WMS less or equal 3, total WBCC increased by 15.3% and by 32.7% in patients with increased WMS > 3 compared to baseline values.

Conclusion: Our results suggest that an acute inflammatory process may be present in patients with positive ESE and that stress induced m.i. accelerated inflammation which is demonstrated throughout significant increased in leucocite and neutrophil count.

P2231 Diagnostic precordial cardiac ultrasound: any effect of somatic DNA in humans?

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Background: In vitro studies show DNA damage in cells exposed to ultrasound in the frequency and power range of current cardiac diagnostic use. These effects Background: In vitro studies show DNA damage in cells exposed to ultrasound in the frequency and power range of current cardiac diagnostic use. These effects can be magnified by high mechanical index imaging amplifying cavitation phenomena underlying DNA damage. Comet assay is a sensitive method to detect DNA damage.

Aim: to assess the effects of diagnostic cardiac ultrasound on DNA of circulating lymphocytes.

Methods: 14 patients (7 males, age= 65 ± 9 years) referred for a diagnostic echocardiogram were scanned under standardized imaging conditions (Agilent Philips Sonos 5500, S3 1.6/3.2 MHz transducer, 2D imaging mode, harmonic fusion, Mechanical Index=1.6, total imaging time=30 minutes). Peripheral blood samples for Comet assay were obtained before (baseline), after 30' ultrasound scanning (ultrasound on), and 30' following the end of the exposure (ultrasound off). Comet assay was scored from 1 (= mild damage) to 4 (= severe damage). 100 lymphocytes were assessed for each stage in each patient, and the global Comet score per patient was the sum of individual cell scores.

Results: Comet damage score was 19±10,3 (mean±SEM) at baseline, 27.1±7.7 with ultrasound on and 29.6±14.7 with ultrasound off. Number of damaged cells (any Comet score) was 10±5 at baseline, 12.5±4 with ultrasound on and 14.9±6 with ultrasound off.

Conclusion: At frequency, power and exposure duration commonly employed in clinical practice, diagnostic cardiac ultrasound does not usually induce a significant DNA damage in circulating lymphocytes, even when aggressive imaging with high mechanical index is utilized.

P2232 The effect of coronary angioplasty on left atrial mechanical functions

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Background: Left ventricular stroke volume is considered to be composed of the left atrial (LA) passive emptying volume, active emptying volume and conduit volume. In the initiation of left ventricular dysfunction, a redistribution of left atrial reservoir, conduit and booster functions is a potentially important adaptation mechanism to maintain cardiac output. The aim of this study was to assess the effect of coronary angioplasty on left atrial mechanical functions.

Methods: Left atrial maximal (LAVmax), minimal (LAVmin) and at the onset of systole (LAVp) volumes were measured just before and after 24 hours procedure according to the biplane modified-Simpson method in 20 patients (14 male, 6 female; mean age 51.2±2.7 years) undergoing successfully coronary angioplasty. And following LA emptying functions were calculated: LA passive emptying volume = LAVmax - LAVp, LA passive emptying fraction = LA passive emptying volume/LAVmax, Conduit volume =Left ventricular stroke volume-(LAVmax- LAVmin), LA active emptying volume = LAVp- LAVmin, LA active emptying fraction = LA active emptying volume/LAVp, LA total emptying volume = (LAVmax -LAVmin), LA total emptying fraction = LA total emptying volume/LAVmax.

Results: Coronary angioplasty was applied to left anterior descending artery in 6 patients, left circumflex artery in 8 patients and right coronary artery in 6 patients. LAVmax (18.4±6.7 vs 18.5±6.1 cm^3/m^2), LAVmin (7.7±3.2 vs 7.7±2.8 cm^3/m^2) and LAVp (14.4±5.9 vs 13.5± 5.9 cm^3/m^2) were not significantly different before and after procedure ($p>0.05$). LA passive emptying volume (3.99±1.26 vs 5.01±1.33 cm^3/m^2; $p<0.05$) and passive emptying fraction (0.23±0.06 vs 0.30±0.12%; $p<0.05$) increased significantly after coronary angioplasty. A decrease was found in LA active emptying volume (6.75±3.06 vs 5.84±3.95 cm^3/m^2) active emptying fraction (0.46±0.10 vs 0.38±0.28%) and conduit volume (15.06±9.96 vs 11.60±6.46, p=0.08)) after procedure, but the differences were not statistically significant. LA total emptying volume (10.74±3.68 vs 10.86±3.89 cm^3/m^2) and total emptying fraction (0.58±0.07 vs 0.59±0.09%) were found similar after procedure ($p>0.05$).

Conclusion: The results of this study suggest that coronary angioplasty led to an increase in left atrial passive emptying functions, but a decrease conduit and active emptying functions, and thus total emptying functions remained steadily. And it indicates that coronary angioplasty reverse compensatory redistribution of LA function in patients with coronary artery disease.

P2233 Low reproducibility of two-dimensional echocardiographic image plane positioning

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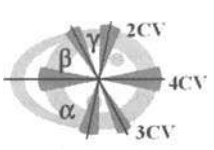
Background In two-dimensional echocardiography, image plane positioning based on anatomical landmarks may not always be reproducible because of random image plane positioning error. At serial examinations, different parts of the left ventricle might be sampled.

Methods Twenty subjects (12 myocardial infarction and 1 mitral valve prolaps patient, and 7 healthy volunteers) underwent transthoracic three-dimensional echocardiography using the TomTec Freehand ® method. Off-line, 2-, 3- and 4-chamber views (CV) were reconstructed based on anatomical landmarks, and angles between image planes measured (see figure). These "virtual examinations" were repeated after 3 weeks.

Results For values and intra- and interobservervariation of alpha (the angle between the 2- and 4-CV), beta (2- and 3- CV) and gamma (3- and 4- CV), see table.

	Alpha	Beta	Gamma
Angle	79,1± 10,3	66,6 ± 8,2	33,7 ± 6,6
Intra-observervariation	-3,2 ± 4,3	4,8 ± 4,6	-1,5 ± 3,9
Inter-observervariation	-1,1 ± 11,9	5,5 ± 11,2	-5,2 ± 8,7

values expressed as mean ± 1 SD, in degrees



Conclusions Based on anatomical landmarks, numerous similar echocardiographic cross-sections can be obtained, however with low reproducibility. This may lead to changes in image plane positioning at serial examinations, sampling of different parts of the left ventricle, and to inconsistencies in wall motion analysis and two-dimensional volume measurements.

P2234 Three-dimensional aortic flow profiles after aortic valve replacement

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Background/Objectives: Three-dimensional (3D) echocardiographic reconstruction can provide dynamic 3D images of intracardiac color flow. Fluid dynamic characteristics of the valve are known to be related to complications such as haemolysis, valve thrombosis, thromboembolic events, calcification and prosthetic valve endocarditis. The aim of the present study was to visualize turbulent stress during systole downstream of the aortic valve and to compare normal and artificial aortic flow profiles.

Methods: Transesophageal echocardiography was performed intraoperatively in patients with normal aortic flow (n=15) and after aortic valve replacement with different types of prostheses (n=20). 3D flow visualization was obtained by the EchoAnalyzer software with improved orientation and angle correction which was developed by our institutions.

Results: Normal aortic flow showed a nearly parabolic profile with peaks slightly laterally displaced from the center. Typical downstream flow profiles could be visualized in artificial aortic valves. For example Star-Edwards showed a pattern with negative velocities in the centre surrounded by high positive velocities (like a king's crown). In Medtronic Hall negative and positive velocities were divided approximately along the diameter (like a diadem). Downstream of St. Jude Medical two high velocity peaks were separated by a nearly linear gap along the diameter (like a bishop's mitra).

Conclusion: 3D reconstruction opens new perspectives for non-invasive diagnosis of prosthetic valve function since it discloses complex flow patterns in patients. Up to now measurements of flow profiles could only be achieved in in-vitro experiments.

NOVEL APPROACHES IN MYOCARDIAL SCINTIGRAPHY

P2235 In vivo monitoring of the fate of transplanted indium-111-labeled endothelial progenitor cells in a rat model of myocardial infarction

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Endothelial progenitor cells (EPCs) can contribute to neovascularization of ischemic heart tissue. Infusion of ex vivo cultivated EPCs was shown to improve vascularization and left ventricular function after myocardial ischemia. At present, the fate of transplanted EPCs has been monitored by DiLDL-labeling or viral infection with GFP or LacZ. However, both techniques are limited by the need to sacrifice the animal, which precludes its use in humans. Therefore, we investigated whether radioactive labeling with Indium-111 is a possible tool to monitor the distribution and the homing of EPCs in vivo.

Human EPCs were isolated out of peripheral blood and were characterized by the expression of endothelial marker proteins (KDR, VE-cadherin, eNOS). After 3 days of culture, EPCs were detached and radioactively labeled with Indium-111-oxin (10 MBq/10(6) EPCs in 1 ml EBM medium without supplements). EPCs incorporated about 79±2% of the applied radioactivity. Control experiments confirmed that the viability of the EPCs was not affected by the labeling procedure.

After removal of the free radioactivity by centrifugation, EPCs were injected in sham-operated or infarcted athymic immunodeficient nude rats and scintigraphic images of the animals were acquired using a gamma camera. Images were continuously obtained over the first hour and repeated at 24 h, 48 h, and 96 h after injection. Then, the animals were sacrificed and specific radioactivity was measured in different tissues. 24 h to 96 h after i.v. injection, the majority of EPCs was localized in the spleen and liver. After 96 hours, only 1.01±0.29% of the radioactivity was detected in the heart of sham operated animals. The ratio of specific radioactivity in heart to peripheral muscle tissue was 1.05±0.16 in sham-operated animals. Following the induction of myocardial infarction by ligation of the LAD, this ratio increased to 1.69±0.39. Similar findings were obtained when radioactive EPCs were injected directly into the left ventricle: the heart to muscle radioactivity ratio increased from 1.6 in sham-operated animals to 4.0, when EPCs were infused 24 hours after infarction.

Conclusion: Radioactive labeling with indium-111 is a feasible method to detect the fate of transplanted progenitor cells in vivo, which could also be applicable to the sequential clinical monitoring of cell therapy. Initial results suggest that only a minor portion of total EPCs are detected in the myocardium under basal condition, whereas myocardial infarction profoundly increased cardiac homing of EPCs.

P2236 Effect of coronary revascularization on myocardial perfusion, function and wall thickness as assessed by quantitative gated SPECT

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The development of quantitative gated SPECT (QGS) enables the assessment of LV perfusion, function and wall thickness by a single examination. Accordingly, QGS was applied to assess the benefit of coronary revascularization in patients with CAD; 120 of those patients were evaluated before and 6 months after elective coronary revascularization. With coronary revascularization, a significant improvement was observed in global EF (49±12 to 52±12%; p<0.001). In 187 revascularized segments, reversibility score (0.8±0.6 to 0.2±0.4; p<0.0001), rest defect score (0.8±0.8 to 0.5±0.6; P<0.0001), wall motion asynergic score (1.1±0.9 to 0.8±0.8; p<0.0001), and end-diastolic wall thickness (8.1±1.3 to 8.6±1.5; p<0.025) improved significantly. Even in 101 non-revascularized segments, reversibility score (0.3±0.5 to 0.1±0.3; p>0.01), wall motion asynergic score (0.8±0.9 to 0.5±0.8; p<0.0001) and end-diastolic wall thickness (8.0±1.3 to 8.5±1.6; p<0.001) also improved significantly. In 43 of these non-revascularized segments, in which the improvement of LV wall motion was detected, the incidence of >90% stenosis (22/43 vs 15/58; p<0.01) and collateral circulation (34/43 vs 15/58; p<0.0001) were higher than in 58 segments in which no improvement of LV wall motion was observed. These results indicate that improvement in myocardial ischemia, hibernation and LV function with coronary revascularization can be assessed in detail by applying QGS. In particular, the beneficial effects were demonstrated even in the non-revascularized segments through good collateral circulation in which blood flow was improved by revascularization.

P2237 Reduced cardiac sympathetic innervation contributes to elevated proinflammatory cytokines levels in patients with congestive heart failure

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Background: In heart failure (HF) both plasma and myocardial tissue levels of cytokines are increased. Experimental animal studies showed that cytokines production might be regulated in part, by sympathetic nervous system (SNS) stimulation of cardiac beta-adrenergic receptors. The cardiac response to sympathetic stimulation is impaired in HF and this may contribute to elevated levels of circulating cytokines. The cardiac fixation of 123-Metaiodobenzylguanidine (MIBG) a norepinephrine analogue, was developed to visualize sympathetic innervation, has the potential to mirror the whole myocardial adrenergic pathway disintegrity and has been found to be reduced in HF.

Objectives: We evaluated the relationship between MIBG cardiac uptake and circulating levels of pro-inflammatory cytokines in patients with idiopathic dilated cardiomyopathy (IDC).

Methods: Thirty-seven patients (7 women, mean age 54 ±11,3 y) with angiographically proven IDC, NYHA class II-III, with Left Ventricular ejection fraction (LVEF) 31,1 + 8,1%, underwent a planar MIBG study and early (10 min) and late (4 hour) heart to mediastinum uptake ratio and washout rate were calculated. Twenty age-matched normal (N) individuals who served as a control group underwent the same procedure. Blood sampling of all patients with IDC for circulating plasma levels of Interleukin -1(IL-1), Interleukin-6(IL-6), TNF-a and its soluble receptors sTNFr1 and sTNFr2 were measured by immunoassay. None of study pts were on beta-blockers or suffered from diabetes mellitus.

Results: The IDC group had significantly reduced MIBG uptake values at 10 min (1,6 ±1.15 vs 1,91 ±0,08, p<0,001) and 4 hrs (1,48 ± 0,17 vs 1,84 ±0,12, p<0,001) and increased WO (7 ± 4%vs 3 ±3%, p<0,005), compared to the control group. Univariate analysis showed that in the patients' group early and late MIBG uptake correlated significantly with NYHA class(r=-0,70,p<0,001 and r=-0,63, p<0,001), LVEF (r=-0,38,p=0,05 and r= -0,34 p=0,01), IL-1 (r=-0,53, p=0,01 and r=-0,50, p=0,01) and sTNFr2 (r=-0,70, p=0,001 and p=-0,61, p=0,001) respectively.Multivariate regression analysis revealed that MIBG at 4 hours was independently associated with sTNFr2 (p=0,01).

Conclusions: The reduced cardiac sympathetic innervation in CHF is related to elevated circulating IL-1 and sTNFr2 levels. The impaired response to increased sympathetic stimulation in CHF may be accompanied by a chronic inflammation state, which further leads to a vicious cycle and cardiac function deterioration.

P2238 Calculation of normal limits of left ventricular ejection fraction and volumes using gated SPECT: the influence of isotope, gender and body habitus

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Introduction: Single photon emission computerised tomography (SPECT) with 201Tl or 99mTc agents has an important role in patients with coronary artery disease(CAD). Gated SPECT provides data on left ventricular (LV) function, including LV ejection fraction (LVEF), LV end-systolic (LVESV) and LV end-diastolic volumes (LVEDV).

There is incomplete information on the role of influencing factors on gated SPECT, with few studies examining normal populations. The role of body habitus on LV functional measurements is observational, with higher LVEFs and smaller volumes noted in smaller hearts. Higher LVEFs have been noted in women.

The objectives of this study were to (1)determine normal values for LVEF in men and women; (2)to determine if either tracer may be used to estimate LVEF; (3) to determine if height, weight and gender impact on LVEF and (4) to determine if the effect of gender on LVEF is due to differences in body habitus between men and women.

Subjects: Subjects met the following criteria: (1) no past history of CAD;(2)normal resting ECG;(3) normal stress test;(4) normal myocardial perfusion and wall motion on SPECT.

Results: 245 patients (106 men, 139 women, mean age 52.7 ± 9.2 years met the entry criteria. The mean LVEF was 60.0 ± 9.5%.

Mean weight and height were higher in men ($p<0.0005$). The LVEF was smaller in men (55.5% vs. 64.5%, $p<0.0005$). LVEDV and LVESV were higher in men($p<0.0005$).

Measurements of LV volumes and LVEF were similar when either isotope was used.

LVEF correlated in a negative manner with weight($r=-0.360$, $p<0.0005$) and height ($r= -0.512$, $p<0.0005$). The relationship of LVEF with weight ($r= -0.252$, $p=0.003$)and height existed only for women ($r= -0.340$, $p<0.0005$) Both LVEDV and LVESV correlated with height and weight, again only in women ($p<0.0005$).

A derived equation connecting LVEF, weight and height in our female population was: LVEF = (280 ± 74) x weight -0.1880 x height -1.1626

Conclusions 1. The normal mean LVEF in men is 55.5 ± 7.7% and 64.5 ± 8.9% in women.

2. Either thallium or technetium tracers may be used measure LV function.

3. There is a negative relationship of both height and weight with LVEF. This relationship is present only in women. This relationship is probably explained by differences in stature between men and women. A height of 1.68 m represents the 90th centile in women but only the 20th centile in men. Similarly, a weight of 80 kg is the 75th centile in women but only the 30th centile in men.

LVEF in women will be overestimated in women. This can be corrected for by use of our formula.

P2239 Stress scintigraphy with dual isotope imaging can accurately document ischaemic preconditioning

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Background: Ischemic preconditioning (IP) induced by exercise (EX) has been well documented by electrocardiography. We assessed the contribution of myocardial scintigraphy, which can be expected to provide more quantitative information.

Methods: Twenty one patients (pts) with angiographically proven coronary artery disease (CAD), normal ventricular function and chronic stable angina underwent two treadmill (TR) EX tests with tomographic perfusion studies, using thallium-201 (TL) for the first study and tetrofosmin-Tc 99m (TET) for the second 30-60 minutes later, followed by rest perfusion study using TET, 4 hours later. Pts with a history of previous myocardial infarction, unstable angina or previous CABG or PTCA were excluded. The first TR EX was symptom limited and the second was terminated at the same time. TL and TET were injected at the same EX time for both studies. The mean age was 64.1±9 years (19 male, 2 female). Three, two and single vessel disease were equally distributed. The distribution of TL and TET uptake was analysed qualitatively as follows: anterior, septal, apical, inferior and lateral segment. The images were graded on a 5-point scale 0 (no uptake) to 2 (definitely reduced) and 4 (normal). The score was derived by summing the uptake of the segments. Also the tomographic images were analysed quantitatively (Bull's eye method), to yield total defect size. Differences between the two TR EX tests were compared.

Results: Maximum ST depression did not differ significantly between 1st and 2nd study 2.2±1.04 vs 2.2±1.4 (NS); the time in seconds of onset of ischemic changes was 282±152 vs 328±177 respectively ($p=0.01$) and the time of the angina 228±94 vs 265±103 ($p=0.01$). The score of EX perfusion was 22±3 in the 2nd study vs 17.5±5 ($p=0.0001$) and the total defect size was 14±5.9 vs 18±5.72 in the first ($p<0.0001$).

Conclusions: a. Exercise-induced IP can be documented by stress scintigraphy. b. The perfusion improvement in the second EX study is much greater than that potentially attributable to differences of myocardial uptake between Tl-201 and TET.

P2240 Relationship between extent of denervated viable myocardium, electrophysiologic abnormalities and outcome after acute myocardial infarction

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Objectives: This study aimed at investigating the correlation between sympathetic denervation of viable myocardium in the risk area of AMI using 201Tl/123I-MIBG scintigraphy, and the electrophysiologic (EP) disturbances predisposing to ventricular arrhythmias. Methods: 67 consecutive post-AMI patients (58±11 y.o., 49 m, thrombolytic therapy: 28,4%, Primary PTCA/Stenting: 55,2%). Rest 201Tl and 123I-MIBG SPECT were quantitatively analysed using polar maps. Scintigraphic defects were identified by using a threshold of 50% of the maximum pixel value. Mismatch area corresponding to viable but denervated myocardium was obtained by the difference between defect sizes. EP studies focused on the detection of 3 classes of abnormalities potentially related to genesis of ventricular arrhythmias: 1. delayed depolarization, using signal averaging EKG (QRS width, terminal RMS, terminal LAS); 2. delayed repolarization, by rest EKG measurements (QTc interval, spatial QT dispersion); 3. imbalance of cardiac autonomic tone by heart rate variability analysis in Holter. Frequency of ventricular premature couplets (VPCs), couplets, salvos was also derived from Holter. Follow-up information was obtained by mail/phone every 6 months.Results: The 201Tl and 123I-MIBG myocardial scintigraphy defect sizes were respectively 14.3 ± 16.4% and 38.4 ± 22.2%, resulting in a mismatch area of 25.8 ± 16.3%. The mismatch size was mildly, but significantly correlated with prolonged repolarization process assessed by QTc interval ($p<0.001$, $R = 0.4$) and with delayed depolarization evaluated by RMS signal ($p<0.01$, $R = 0.37$). Follow-up period was 4.3 ± 1 years, and only 2 patients presented cardiac death (mismatch sizes of 47.4% and 36.9%). Conclusions: In pts after early agressive revascularization for AMI, the amount of viable but denervated myocardium in the infarction area is correlated to slow depolarisation and repolarisation processes that could contribute to the genesis of late potentials. Despite these findings, the observed long-term prognosis was excellent.

P2241 Effects of timing of functional recovery after revascularization on rest 201Tl SPECT accuracy in patients with chronically occluded LAD

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Introduction: Despite the growing interests on the revascularization (REV) of patients with chronically occluded vessels (COV), few data have been published about rest TL SPECT (TL) in predicting functional recovery (FR), and in particular the effects of the timing of FR on its accuracy. We selected patients with chronically occluded LAD since the major impact of LAD and anterior myocardial territory on global left ventricular function and prognosis.

Methods and Materials: From a consecutive series of patients undergoing evaluation of myocardial viability at our Institute, we selected patients (pts) undergoing REV of chronic occluded LAD (> 1 month). Thus 27 pts(58±12 ys, 3 female) represented our final population. They underwent rest-redistribution 201Tl SPECT and echocardiogram at rest before revascularization, at three months (3M, all patients) and 1 year (12M, 18 patients) after revascularization. Different cut-offs for images at rest were tested according to the outcome at 3 and 12 M.

Results: Regional FR was observed in 60/112 (53%) at 3M and in 50/73 (68%) segments at 12M ($p < 0.05$ vs 3M). Regional WMSI changed from 1.99 ± 0.49 to 1.61 ± 0.5 at 3M ($p < 0.001$ vs baseline), to 1.42 ± 0.43 at 12M ($p < 0.001$ vs baseline; $p < 0.01$ vs 3M). Global ejection fraction improved from 40 ± 9% to 45 ± 10% at 3M ($p < 0.0001$ vs baseline) to 48 ± 7 at 12M ($p < 0.0001$ vs baseline; $p < 0.05$ vs 3M). Among the different tested thresholds, 60% of Tl uptake conferred the best accuracy at 3M (69%) whereas 55% of Tl uptake conferred the best accuracy at 12M (66%).

Conclusions: Our study demonstrated that regional and global ventricular functional recovery is only partially completed at 3M in comparison with 12M, in patients with chronic occluded LAD undergoing revascularization. The observed late functional recovery at 12M explained the better accuracy observed for lower cut-offs at 12M in comparison with 3 M. Thus a cut-off of 55% instead of 60% should be used to better predict long-term functional recovery after revascularization of chronically occluded LAD.

P2242 Recovery of left ventricular function by carvedilol is associated with improvement of myocardial perfusion in acute myocardial infarction

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Background and purpose: Carvedilol has been shown to reduce mortality and ischemic events after acute myocardial infarction (AMI) through beta-blocking and antioxidant actions, but the mechanism of beneficial effects is not fully elucidated. We serially studied the effects of carvedilol on left ventricular function as well as myocardial perfusion using Tc-99m tetrofosmin ECG-gated SPECT (TF) in patients with AMI.

Methods: Forty-eight patients who underwent successful percutaneous coronary intervention (PCI) for their first anterior AMI were recruited. A few days after PCI, they were prospectively assigned into Carvedilol (N=24) and Control (N=24) groups. Baseline TF was performed 10-14 days (sub-acute), and was repeated 3 months (chronic) after the onset. Myocardial perfusion was evaluated from ECG-gated end-diastolic polar map image. Myocardium was divided into 17 segments for analysis of regional perfusion and segmental score was graded by 5 degrees (0: normal - 4: defect). The total defect score (TDS) were calculated as the sum of defect scores. Left ventricular ejection fraction (LVEF) was obtained using automated quantitative method.

Results: Baseline characteristics were similar between Carvedilol and Control (age: 60.4±10.6 vs. 61.5±9.9 years, CPK: 4998±2638 vs. 4890±2206 IU/L, sub-acute TDS: 33.7±5.5 vs. 33.3±4.7, LVEF: 41.9±11.7 vs. 42.5±11.2%, n.s.). Concomitant therapy, including aspirin, angiotensin-converting enzyme inhibitors, nitrates and diuretics were similar in both groups. There was no cardiac events (cardiac death or re-hospitalization) during the three months. At chronic TF study, heart rate decreased (-6.3± 8.0 vs. +1.3±12.0/min, p=0.02), LVEF improved (+7.7± 9.7 vs. +1.8±9.2%, p=0.04) and TDS decreased (-2.7±4.7 vs. 0.0±4.3, p=0.03) in Carvedilol treatment group compared with Control.

Conclusion: Carvedilol improves both LV function and myocardial perfusion in AMI with reperfusion therapy. Beta-blocking action and vascular endothelial protection through antioxidant action might be mechanisms for its beneficial effects.

P2243 Accuracy of quantitative myocardial stress perfusion imaging in the detection of coronary allograft vasculopathy after heart transplant

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Background and Objectives: Coronary allograft vasculopathy (CAV) is the main factor that limits long-term survival after heart transplantation (HTx). We evaluated the accuracy of 2 quantitative methods to assess flow maldistribution from myocardial perfusion single photon emission tomography (SPECT) imaging.

Methods: 88 HTx recipients (mean age 51±12 yrs) underwent dipyridamole-stress sestamibi imaging at a mean interval of 40 months from HTx. Stress and rest images were quantitatively analyzed by 2 methods (Q1 and Q2) and compared with a sex-matched normal database. The database was obtained from a HTx population with one year post-HTx SPECT, normal coronary angiography and normal resting echocardiography, without rejection episodes. Q1 analyzed myocardial segments, matched to the coronary-tree distribution, in the bull's eye map. The size of perfusion defects was expressed as percent of count activity in a vascular territory and in the whole left ventricle. Q2 determined the segmental distribution of radioactivity from short axis slices. The computer expressed myocardial uptake of 16 segments in the apical, middle and basal cardiac slices as percent of count activity with respect to maximum activity. Data were also qualitatively (QL) evaluated by 16 segment analysis and a 4 point perfusion score. Q1, Q2 and QL analyses were compared with coronary angiography; CAV was classified according to Gao et al.

Results: Q1 analysis showed a better accuracy than Q2 and QL to identify CAV, very high sensitivity and negative predictive value and a good specificity. Accuracy of Q1, Q2 and QL analysis are shown in the table.

values in percent	Q1	Q2	QL
Sensitivity	100	77	100
Specificity	83	60	57
Positive predictive value	50	25	29
Negative predictive value	100	94	100
Accuracy	85	63	64

Conclusions: Quantitative analysis of perfusion stress imaging, in conjunction with a normal database of HTx recipients, provides a good accuracy in CAV detection, which favourably compares with previous SPECT or stress-echocardiography studies. This approach seems appealing in risk stratification and prediction of prognosis of HTx patients.

P2244 Non-invasive quantification of the total ischaemic burden – correlation with clinical and angiographic findings

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Background: Not only the presence/absence of myocardial ischemia, but also the extent of the ischemic burden provides important information for clinical decision making and prognosis. We tested the hypothesis that a simple ischemia score derived from myocardial perfusion SPECT (MPS) in a large patient cohort reflects the severity of coronary artery disease and thus adds evidence for clinical decision making.

Methods: 570 consecutive patients who underwent dual isotope (Tl-201-rest/Tc-99m sestamibi stress) MPS and subsequent coronary angiography (cath) were evaluated. MPS was interpreted by visual scoring of perfusion images using a 20 segments' model and a scale of 0 to 4. Summed scores were calculated by adding the 20 SPECT segment scores. A summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS=SSS-SRS, [extent of ischemia]) were derived. A stenosis >74% on cath was considered significant. We then calculated receiver operating curves (ROC) to define SDS, that best divided the pts in two groups of having relevant coronary artery stenoses.

Results: ROC revealed an SDS of <3 and >=3 to be the best cutoff of having small amount and relevant amount of ischemia, respectively. For results see table.

Small versus relevant amount of ischemia

	SDS<3 (200)	SDS>=3 (370)	p
Angina during test	58 (29%)	187 (51%)	<0.001
Ischemic ECG	31 (16%)	156 (42%)	<0.001
n of vessels with >74% stenosis	0.9 ± 1.0	1.6 ± 1.0	<0.001
No significant stenosis	113 (57%)	33 (9%)	<0.001
Triple vessel disease	22 (11%)	91 (25%)	<0.001
LAD stenosis >74%	70 (35%)	240 (65%)	<0.001
Proximal LAD stenosis >74%	29 (15%)	107 (29%)	<0.001
Ejection fraction (by cath)	65 ± 14%	62 ± 13%	0.03

n=number

Conclusion: The extent of ischemia (SDS) is easily quantified by MPS and is a good non-invasive predictor of the severity of coronary artery disease. In contrast to other signs of ischemia such as angina and ST-changes, the 20-segment system allows localization and non-invasive quantification of the ischemic burden which is important for clinical decision making.

PERCUTANEOUS CORONARY INTERVENTION: ADJUNCTIVE THERAPY, COMPLICATIONS

P2245 Predictors of CK-MB release in patients undergoing percutaneous coronary intervention with stents and GP IIb/IIIa inhibitors

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Background: Coronary stent implantation, the main mode (up to 90%) of percutaneous coronary intervention (PCI), is associated with higher CK-MB release (compared to balloon angioplasty), largely due to side branch closure and distal micro and macro thromboembolism. GP IIb/IIIa inhibitor (GPI) use during stenting has been shown to decrease CK-MB release. Reliable predictors of CK-MB release in the era of stenting and GPI have not been described.
Methods: We analyzed 1026 consecutive patients without myocardial infarction (MI) undergoing stenting, with normal baseline values of CK-MB, who received GPI during PCI. Among these, 874 (85%) patients had normal CK-MB release (<16 U/L) and 152 (15%) had CKMB elevation higher or equal to 16 U/L, with 1-3x normal in 11%, 3-5x normal in 2% and >5x normal in 2%. Significant characteristics are shown in the table.
Results: Among the clinical and angiographic characteristics, specific type of GPI, hypertension, diabetes mellitus, angina class, peripheral vascular disease, cerebro-vascular accident, previous MI, bypass surgery, vessel intervened, ACC/AHA B2/C lesion, restenotic lesion, calcification, and dissection were similar between the two groups. Multivariate predictors of CK-MB release: age ($p<0.008$), female sex ($p<0.04$), LVEF ($p=0.06$), slow-flow ($p<0.0001$) and side branch closure ($p<0.0006$).

Characteristics	Normal CKMB (n=874)	Elevated CKMB (n=152)	p
Age (yrs)	64.8±11	68.1±11	0.001
Female sex (%)	30	40	0.01
Lesion length (mm)	12.4±6.1	14.4±13	0.003
Thrombus (%)	2.2	3.3	0.001
Side branch closure (%)	0.2	9.2	0.001
Slow flow (%)	2	14.4	<0.0001

Conclusions: In the era of stent and GPI use during PCI, the incidence of peri-procedural CK-MB elevation seems to be lower than historical controls of stenting without GPI (up to 30%). Markers of diffuse atherosclerosis (such as advanced age and long lesion) and procedural complications continue to be the predictors of CK-MB release. Based on the above observation, a prospective model was constructed for same day discharge (14-15 hours post PCI) after angiographical successful stenting and 12-hour GPI infusion.

P2246 is clopidogrel inferior to ticlopidine in preventing subacute stent thrombosis?

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Background: Platelet inhibition with aspirin and thienopyridines is essential for prevention of subacute (>24 hours) stent thrombosis (ST). Ticlopidine and clopidogrel have been shown to be similary effective in the prevention of ST during the first 30 days. The purpose of the present study was to determine ST in a retrospective analysis comparing ticlopidine and clopidogrel treatment.
Patients and methods: A total of 4453 patients were included in the present analysis. In a first observation period from Nov. 1995 to Jan. 1999 (group 1, n=1806 patients) aspirin 100mg/d plus ticlopidine 2x250mg/d (for 2 weeks) was given, whereas in a second period from Feb. 1999 to Jan. 2002 (group 2, n=2647 patients) aspirin 100mg/d plus clopidogrel 75mg/d (for 4 weeks, after a loading dose of 300mg) was administered.
Results: Subacute ST was observed in 65 patients, 15 (0.83%) in group 1 and 50 (1.89%, p=0.003) in group 2. ST occurred after a mean of 8.7 days in group 1 and 22.3 days (p=0.04) in group 2, respectively. Late ST (>28 days) was found only in clopidogrel- (n=17), but not in ticlopidine-treated (p=0.009) patients. 34% of all ST in group 2 occurred late (>28 days) after stent placement (mean= 50.1 days, range 28-110 days). The only predictor for late ST was TIMI flow 0 before PCI (p=0.04). Procedural data in patients with ST were similar in those with ticlopidine- and clopidogrel-treated patients (stenosis severity before and after intervention, lesion length, lesion type A-B-C, vessel diameter, stent length, maximal inflation pressure, TIMI flow before and after intervention and persistent dissection after stenting). The use of GPIIb/IIIa-antagonists and the indication (acute infarction, unstable, stable angina) for percutaneous coronary intervention (PCI) was comparable in the two groups with ST.
Conclusions: The rate of subacute ST was significantly lower in ticlopidine- than clopidogrel-treated patients. Late ST (>28 days) only occurred in patients receiving clopidogrel, especially in those with TIMI flow 0 prior to PCI. These data suggest that clopidogrel is less effective in preventing subacute ST and is associated with the phenomenon of late ST. Thus, patients after coronary stenting should receive either ticlopidine or higher doses of clopidogrel for prevention of ST.

P2247 How rapidly are platelets inhibited by a 300 mg clopidogrel loading dose given at the time of intervention compared to pretreatment

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Background: The effect of a 300 mg loading dose of clopidogrel administered in the catheterization laboratory at the time of coronary stenting versus pretreatment on the kinetics of platelet inhibition is unknown.
Methods: Patients undergoing elective stenting (n=103) were treated with either 300 mg clopidogrel at the time of the procedure (TP) or at 3-6 (3-6 pre) or 24 hours (24 pre)prior to the prcedure. Platelet-rich plasma aggregation (PPA) (5μ mol ADP), and flow cytometry of platelet receptors were serially performed. All patients received 325mg aspirin and 75mg clopidogrel daily post procedure. GP IIb/IIIa inhibitors were not used.
Results: PPA was most inhibited at 2 and 24 hours post-stenting by loading 24 hours prior to the procedure ($p<.05$) (see table). PAC-1 (mean fluorescence intentsity) was mildly reduced by clopidogrel (78±46, baseline, 62±40, day 5, $p<0.05$). No effect was seen on platelet-leukocyte aggregate formation.

	PPA (% Inhibtion)		
Time of assessment	TP	3-6 pre	24 pre
2h post	14± 4	18 ± 7	35 ± 15*
24h post	35 ± 11	33 ± 16	47 ± 23*
5d post	31 ± 13	41 ± 12	41 ± 14

*$p<.05$ compared to TP and 3-6 pre

Conclusion: Pretreatment with 300 mg clopidogrel 24 hours prior to intervention gives the best early post procedure inhibition of ADP-induced plateelt aggregation. Loading with clopidogrel followed by 75mg daily mildly reduces activation of GPIIb/IIIa but does not affect the formation of platelet-leukocyte aggregates.

P2248 Abciximab in percutaneous coronary intervention in patients over 75 years of age

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Background: The benefit of abciximab administration in patients (pts) submitted to coronary percutaneous intervention (PCI) is established in the entire clinical spectrum of coronary artery disease. Recently, trials evaluating the benefit of the association of abciximab with fibrinolytics revealed a high rate of hemorrhagic complications in pts over 75 years of age. On the other hand, the influence of abciximab in the sub-group of pts over 75 submitted to PCI has not been specifically evaluated.
Objectives: Evaluation of the efficacy and safety of abciximab in pts over 75 submitted to PCI.
Population and methods: 168 pts over 75 years submitted to PCI were studied retrospectively. Two groups were considered: with abciximab (G1: 88 pts, 57 men, mean age 78 years) and without abciximab (G2: 80 pts, 54 men, mean age 78 years). No significant differences were found in the two groups regarding demographic characteristics, indication for intervention, severity of coronary artery disease and left ventricular systolic function. There was no difference between the two groups in stent use (G1: 85% Vs G2: 84%) or multivessel intervention (G1: 38% and G2: 34%). The efficacy of abciximab was evaluated by the combined occurrence of death, myocardial infarction (MI) or urgent revascularisation (UrgRev) before discharge and the combined occurrence of death or MI at one year. Safety was evaluated by the frequency of hemorrhagic complications, isquemic stroke and thrombocytopenia.
Results: The table shows the results of clinical events in the two groups.

		With Abciximab	Without Abciximab	p
In-hospital	– Death/MI/UrgRev	0%	1.25%	0.962
	– Complications			
	Hemorrhagic	10.2%	3.75%	0.184
	Arterial access	6.8%	3.75%	0.590
	Hemorrhagic stroke	0%	0%	–
	Other major	3.4%	0%	0.279
	Ischemic stroke	0%	3.75%	0.211
	Thrombocytopenia	3.2%	0%	0.740
1-year follow-up	– Death	0%	6.6%	0.183
	– MI	2%	4.9%	0.757
	– Death/MI	2%	9.9%	0.194

Conclusion: In the present population of pts over 75 years submitted to PCI, the administration of abciximab was associated with a trend for increased risk of bleeding but better efficacy.Events in the two groups

P2249 Nitroglycerine infusion after coronary angioplasty does not influence a short-term outcome

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Background.The influence of nitroglycerine infusion on patients after elective coronary angioplasty is not established, although this regimen is routinely used in some centers.

Purpose: Nitroglycerine Administration after Percutaneus Intervention (NAPI) study was testing efficacy of routine nitroglycerine infusion in the 1st day after PCI (percutaneus coronary intervention) in a randomized single-centre clinical trial.

Methods and Results: We randomly assigned 100 patients who were undergoing elective PCI to treatment with nitroglycerine (50 patients, aged 58±6 years, dose up to 100 micrograms/min under blood pressure control) or placebo (50 patients, aged 57±5 years; p=NS). Patients with acute myocardial infarction, known intolerance to nitrates, and hemodynamic instability during PCI were excluded. Patients who were randomized to placebo group had possibility to receive nitroglycerine infusion according to attending physician's discretion. Endpoints were assessed in hospital and after 30 days, incl.: cardiac death, myocardial infarction, postprocedural chest pain unstable angina and repeated PCI.

There were no differences during inhospital stay between those receiving nitroglycerine and receiving placebo, respectively: deaths (0% vs 0%, p=NS), myocardial infarctions (0% vs 0%, p=NS), postprocedural chest pain (0% vs 2%, p=NS), repeated PCI due to unstable angina (0% vs 2%,p=NS).

Similar, outhospital follow up at 30 days after procedure revealed no significant differences in cardiac events between studied groups.

Conclusions: Routine use of intravenous nitroglycerin after PCI has no influence on both inhospital and short-term outhospital outcome, inluding cardiac death, myocardial infarction, postprocedural chest pain, unstable angina and repeated PCI.

P2250 Statins in general and atorvastatin in particular do not affect platelet inhibition with clopidogrel during coronary stenting

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Background: Platelet activation following stent implantation is well documented and may affect both short- and long-term clinical outcomes. Clopidogrel is widely used to produce sustained platelet inhibition in order to prevent further ischemic events in patients with atherothrombosis. Certain clinical scenarios exist when treatment with clopidogrel is combined with the chronic use of statins. It has been recently reported that some statins, and atorvastatin in particular, may selectively interfere with clopidogrel, limiting the ability of this ADP-receptor blocker to inhibit platelet function.

Methods: We analyzed the data from the PRONTO (Plavix Reduction of New Thrombus Occurrence) trial, which evaluated platelet inhibition produced by loading dose clopidogrel pre- and post-stenting to determine whether the use of statins influence the ability of clopidogrel to inhibit platelets. Platelets were assessed by conventional plasma aggregometry induced by 5μM ADP and by expression of GP IIb/IIIa (CD41b), and PECAM-1 (CD31) by whole blood flow cytometry at baseline, at discharge, and at day 5 following stent implantation.

Results: Data from 100 patients were analyzed. Twenty-five patients were treated with a statin, (9 of those patients received atorvastatin) and 75 were not on statin therapy. Platelet inhibition by clopidogrel was identical in all groups, and resulted in 35-40% inhibition of aggregation, more than 50% reduction of GP IIb/IIIa expression, and 40-45% reduction of PECAM-1 expression at day 5 when compared with the baseline values. These effects were independent of statin use.

Conclusion: The study results suggest there are no apparent interactions between clopidogrel and statins.

P2251 Comparison of eptifibatide and abciximab in the in-hospital outcomes and thrombocytopenia during percutaneous coronary intervention

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Background: During percutaneous coronary intervention (PCI), glycoprotein IIb/IIIa inhibitors have significantly reduced the incidence of 30-day ischemic events. However, each one of the three currently available agents has different pharmacological characteristics, safety, efficacy and costs. There has not been a direct assessment of whether there are differences between eptifibatide and abciximab in the rates of major adverse cardiac events, major complications and thrombocytopenia.

Methods: A total of 642 patients underwent PCI at our institution between 1/2000 and 5/2001 and were treated with either eptifibatide of abciximab during the procedure. In-hospital clinical outcomes were evaluated. Total thrombocyte counts were performed 2 and 4 hours after initiation of the drug treatment. The selection of a IIb/IIIa inhibitor was arbitrary and left at the discretion of the operator.

Results: Baseline clinical characteristics, concomitant drug treatment and angiographic characteristics were similar between eptifibatide and abciximab. In-hospital death (1.2% vs. 1%, p=0.8), stroke (0%) and target vessel revascularization rates (1.2% vs. 1%, p=0.8) were also similar between the two groups, respectively. Bleeding complications and platelet counts are shown in the table.

	Eptifibatide (n=342)	Abciximab (n=300)	p
Major bleeding (%)	1.7	0.7	0.2
Minor bleeding (%)	4.6	3.0	0.2
Hematoma (%)	7.7	6.3	0.6
Platelet <100,000 cells/L (%)	0.3	6.0	<0.001
Platelet <50,000 cells/L (%)	0	3.3	<0.001
Platelet <20,000 cells/L (%)	0	1.6	0.01
Platelet >50% reduction (%)	0	2.0	0.008

Conclusions: 1) Both agents, eptifibatide and abciximab, proved to have the same rate of in-hospital major adverse cardiac events, bleeding and vascular complications. 2) There was a significantly higher incidence of thrombocytopenia <4 hours after initiation of abciximab, including four patients who developed profound thrombocytopenia (<20.000 cells/L). 3) Although thrombocytopenia was not associated with increased bleeding complications, it triggered immediate cessation of the drug treatment.

P2252 Angiotensin-converting enzyme (ACE) inhibitor treatment of patients with the ACE DD genotype and effect on restenosis after coronary stent placement

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Unexpected results of a recent study including 546 patients suggested that treatment with an ACE inhibitor increased the risk of restenosis after coronary stent placement in the subgroup of subjects carrying the DD genotype of the ACE gene I/D polymorphism (n=91). We tested this finding in a much larger, consecutive series of patients with coronary artery disease who were treated with coronary stenting (n=2222). ACE genotype distribution was in Hardy-Weinberg equilibrium, with 612 patients (28%) typed as DD homozygotes. Of these, 403 (66%) received an ACE inhibitor after the procedure for at least 1 year. Clinical (death; myocardial infarction, MI; target vessel revascularization TVR) and angiographic outcome measures of the DD patients were evaluated during the first year after the intervention and correlated with ACE inhibitor treatment. The occurrence of restenosis (defined as a 50% or greater diameter stenosis) was determined by coronary angiography in 495 DD patients (81%) at 6 months. As shown in the table, treatment of DD carriers with ACE inhibitors did not lead to any risk increase for clinical and angiographic adverse outcomes if compared with the DD patients not receiving an ACE inhibitor.

	+ ACE inhibitor	- ACE inhibitor	P value
Death, 1y (%)	1.7	2.4	0.58
Death or MI, 1y (%)	4.2	6.2	0.28
TVR, 1y (%)	20.6	24.9	0.23
Loss index	0.56	0.56	0.99
Restenosis rate (%)	34.0	31.4	0.55

Clinical and angiographic outcome aftery coronary artery stenting

Conclusion: In line with previous trials which assessed the use of ACE inhibitors as a preventive strategy for restenosis, we did not find any protectice effect in this regard, even not in patients homozygous for the D allele. This result, however, is in contrast with a recent trial showing a negative impact of an ACE inhibitor in patients carrying the DD genotype.

P2253 A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents

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Background: Randomized trials comparing clopidogrel and ticlopidine after coronary stenting with a restricted use of intravenous glycoprotein IIb/IIIa inhibition have reported a higher incidence of thrombotic stent occlusion with clopidogrel at 30 days. The aim of the present study was to compare clopidogrel and ticlopidine with regard to cardiovascular death during long-term follow-up.
Methods and Results: After successful stent implantation during elective or emergency percutaneous coronary intervention, 700 patients with 899 lesions were randomly assigned to receive a four-week course of either 500 mg ticlopidine (n=345) or 75 mg clopidogrel (n=355) in addition to 100 mg aspirin. Concomitant medications included statins in 85% of patients. Cardiovascular death was the primary endpoint and recorded for three years.
Cardiovascular and all-cause mortality were significantly lower in patients assigned to receive ticlopidine. Cardiovascular death occurred in 8 patients (2.3%) with ticlopidine versus 26 patients (7.3%) with clopidogrel (hazard ratio with ticlopidine as compared with clopidogrel, 0.30; 95% confidence interval 0.14 to 0.66; p=0.003). The combined endpoint of cardiovascular death or nonfatal myocardial infarction was present in 19 patients (5.5%) assigned ticlopidine as compared with 40 patients (11.3%) assigned clopidogrel (hazard ratio 0.45; p=0.005). All-cause mortality was 2.6% with ticlopidine but 8.2% with clopidogrel (hazard ratio 0.30; p=0.002).
Conclusions: After the placement of coronary-artery stents in unselected patients, ticlopidine was associated with a significantly lower mortality as compared to clopidogrel. This raises concern about the current practice of substituting clopidogrel for ticlopidine after stenting and highlights the urgent need for further long-term studies on this topic.

P2254 Atorvastatin given at the time of coronary artery stent implantation reduces the systemic inflammatory response

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Successful coronary artery stent implantation (SI) is followed by a marked systemic inflammatory response as indicated by the rise of plasma levels of C-reactive protein (CRP). In turn, persistently elevated levels of CRP after SI are predictive of post-procedural coronary events in both patients with stable and unstable angina. We carried out a prospective study aimed at assessing the acute effect of statin treatment on CRP levels after SI.
We studied 223 patients with stable angina and normal preprocedural CRP levels (<5 mg/L) undergoing single vessel SI. Eighty-five patients were on treatment with statins initiated >6 months before SI (Pre-stat), 62 patients received 80 mg atorvastatin immediately after SI (Stent-stat) and 76 patients did not receive statins neither before or after SI (No-stat). CRP levels were assessed at baseline, 24 and 48 hours after SI.
Demographic, angiographic and procedural variables were similar in the 3 groups and SI was successful in all patients. Total and LDL-cholesterol levels were lower in the Pre-stat than in No-stat and Stent-stat groups (182±34 vs 203±38 and 208±36 mg%, p<0.001 and 108±31 vs 126±36 and 130±29 mg%, p<0.001). Baseline CRP levels in the Pre-stat group were lower than those in the No-stat and Stent-stat groups (2.8±0.8 vs 3.3±0.5 and 3.1±1.2 mg/L, p=0.003). At 24 and 48 hours after SI, CRP levels in the No-stat group were higher than those in the Pre-stat and Stent-stat groups (8.3±10.4 vs 5.1±4.7 and 6.7±9 mg/L, p=0.05 and 16.2±15.7 vs 9±8.5 and 10.8±10.3 mg/L, p=0.005). CRP plasma levels at 24 and 48 hours in the Pre-stat and Stent-stat groups were similar.
Thus, in patients with stable angina undergoing successful SI, high dose of atorvastatin given on the day of the procedure reduces the systemic inflammatory response to a level comparable to that observed in patients pre-treated with statins for >6 months. As high level of CRP after successful SI are predictive of cardiovascular events the reduction of the systemic inflammatory response by high dose of atorvastin may be clinically beneficial.

P2255 Influence of platelet glycoprotein IIIa P1A polymorphism on mean platelet volume and inflammatory response after coronary stent implantation

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Background: The PlA(2) allele of platelet glycoprotein IIIa (PlA) polymorphism has been identified as an independent risk factor for restenosis after coronary stent placement (ST). It's influence on the mean platelet volume (MPV), an indirect parameter for activated platelets, and the inflammatory response after ST is unknown.
Methods: Between September and December 2001 we enrolled 48 patients (44 men, mean age: 64±9 years) before ST. PI(A) polymorphism was analyzed and levels of C-reactive protein (CRP), platelet count (PC) and MPV were determined before ST, 3h, 6h, 12h, 24h, 48h, and 7 days thereafter.
Results: In our cohort the distribution of the genotypes was: 75% for PI(A1/A1), 23% for PI(A1/A2) and 2% for PI(A2/A2)

n=48	P1(A)	before	3h	6h	12h	24h	48h	7 days
CRP	A1(1)	0.2±0.2	0.2±0.2	0.2±0.2	0.3±0.2*	0.6±0.3**	0.9±0.7**	0.9±1.4*
(mg/dl)	A2(2)	0.3±0.2	0.3±0.2	0.3±0.2	0.4±0.3**	0.9±0.6**	1.0±0.7**	0.5±0.4**
PC	A1	231±61	225±55	227±51	230±59	233±57	232±58	251±51
(G/l)	A2	219±50	205±51**	205±52	203±47*	208±44	207±42	234±39
MPV	A1	9.6±1.1	9.5±1.6	9.7±2.0	9.6±1.1	9.3±1.1	9.5±0.9	9.6±1.7
(fl)	A2	9.8±0.9	10.3±2.0	11.4±1.6*	10.2±0.7	10.2±1.0	10.2±0.8	9.8±0.7

(1): genotype A1/A2; (2) genotype A1/A2 or A2/A2. *p<0.05, ** p<0.01

Before ST no differences were found between carriers and non-carriers of PI(A2) concerning levels of CRP, PC and MPV. Independent on the genotype, CRP levels increased after ST. In patients who were homozygous for PI(A1), PC and MPV did not change after ST, while PC decreased significantly and MPV increased significantly in carriers of the PI(A2) allele.
Conclusions: 1. Before ST there are no differences in MPV, PC and CRP levels between carriers and non-carriers of the PI(A2) allele. 2. After ST the inflammatory response is not influenced by the genotype of PI(A) polymorphism. 3. MPV increases and PC decreases in carriers of the PI(A2) allele only. Therefore the increased risk for restenosis in carriers of the PI(A2) allele may be caused by platelet activation.

P2256 Failed coronary stent deployment: single center experience

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Background: Stents have revolutionized percutaneous coronary interventions (PCI) impacting acute and long-term results. Despite the rapid improvement in stent design, failure of stent deployment is not a rare event. Aim: To assess frequency and causes of stent deployment failure (failing in delivery or deployment) in routine clinical practice, as well as short- and long-term outcome in patients (pts) with failed stenting. Methods and results: Between January 1997 and December 2001 stent assisted PCI was performed in 3291 pts. Delivery of total 4896 stents was attempted. Indications for stenting included suboptimal result after balloon angioplasty (65; 43.9%), provisional (50; 33.8%) and bailout stenting (33; 22.3%). A total 175 stents in 148 pts (4.5%) failed to be deployed. Reasons for stent deployment failure were vessel- (severe tortuosity or/and calcification of the lesion) [138; 92%] or stent-related (balloon rupture or failure to inflate the balloon) [12; 8.1%]. Peripheral stent embolization occurred in 10 pts (0.3%). Deployment of another stent instead of the failed one was successful in the majority of pts (106; 71.6%). In 13 (8.8%) pts a second attempt was unsuccessful. In 29 (19.6%) pts no new stent deployment was attempted. In-hospital major adverse cardiac events (MACE) were observed in 6 (4%) pts: emergent coronary artery bypass surgery (3), MI (2) and urgent re-PCI (1). At 1-year follow-up, 16 MACE occurred in 13 pts (8.8%) [6 of them had no stent during the index procedure]: cardiac death (1), MI (2) and TVR (13). One-year event free survival in the whole group was 91.2%. No events were registered in pts with stent embolization. Conclusions. 1. The rate of stent deployment failure in our series was 4.5%. 2. The main reasons for stent deployment failure were unfavorable vessel characteristics. 3. The use of another stent was successful in a high percentage (72%) of cases. 4. Stent failure was associated with favorable short- and long-term results.

P2257 Procedural complications during percutaneous coronary intervention in a 10 year period from 1989 to 1998. Results from the Danish PTCA Register

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Background: Old age has been claimed to be a specific risk in percutaneous coronary intervention (PCI). During the 10 year period from 1989 to 1998 data from all PCI procedures in Denmark were prospectively recorded in a central database, and data have now been analysed with regard to procedural complications occurring within 24 hours after PCI.
Methods: Angiographic baseline characteristics, outcome of PCI and procedural complications were analysed in a total of 13.886 consecutive procedures, performed in 10.896 patients having 19.472 lesions dilated.
Results: The number of procedures per million inhabitants increased sixteen fold from 47 in 1989 to 753 in 1998. Mean age was 59 ± 10.1 year, women were significantly older than men (61 ± 10.2 vs. 58 ± 10.0; p<0.000001). From 1989 to 1998 the mean age increased significant from 56 ± 9.3 to 60 ± 10.5 (p<0.000001), whereas gender ratio remained unchanged 3:1. Multivariate logistic regression analyses of MACE (myocardial infarction=MI, coronary artery bypass grafting=CABG, and death) identified the following independent predictors for procedural complications (table):

MACE	Predictor	Relative Risk	95% C.I.	p
MI	Age	1.02	1.01-1.04	< 0.001
	Female gender	1.43	1.11-1.84	0.006
	Stenting	1.24	1.01-1.54	0.044
CABG	Stenting	0.41	0.31-0.55	< 0.001
Death	Age	1.07	1.05-1.10	< 0.001

In general MACE decreased from 5.0% in 1989 to 2.9% in 1998 (p=0.003). MI occurred in 2.1% of all procedures. The overall procedural related frequency of MI did not decrease during the 10 year period, but in patients < 75 years old the risk decreased (p=0.007), while the risk in patients older than 75 years remained unchanged. CABG decreased significant from 3.2% in 1989 to 0.6% in 1998 (p<0.001). Procedural related mortality remained unchanged around 0.5%.
Conclusion: During a 10 year period (1989-98) total MACE within 24 hours following PCI decreased significantly mainly due to a significant decrease in procedure related acute CABG and the increasing use of stents. Age and gender were independent risk factors for procedural MI, whereas only age was an independent predictor for death.

P2258 What is the adverse event rate of patients awaiting a percutaneous coronary intervention? An 18 month longitudinal study

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Background: The aim of this study was to assess the risk of adverse coronary events (AE) in patients awaiting elective Percutaneous Coronary Intervention (PCI) from a UK population, where the waiting lists for PCI were upto 18 months.
Methods: The observational cohort was composed of 147 outpatients (117 males, median age 59.5 years [range 31-79 years], 69.4% patients had single vessel coronary artery disease (CAD) and 70.7% patients were on a statin) placed on a waiting list for PCI between October 1998 and September 1999. Primary major AE were Death or nonfatal AMI or need for urgent hospital admission due to UA or significant angiographic progression of CAD whilst on the waiting list.
Results: After a median follow-up of 14 months [range 1-25 months], 41(27.9%) patients experienced a major cardiac AE. One patient (0.68%) died, one patient (0.68%) was admitted with an AMI and 13 patients (8.8%) were admitted with UA as emergencies. 26 patients (17.7%) had significant angiographic progression of CAD at the time of their check angiogram prior to PCI. Three of these patients developed a new occlusion and 9 were referred for CABG. Thirteen (8.8%) patients anginal symptoms significantly improved whilst waiting for PCI. Their names were removed from the PCI waiting list. Three (2%) patients at the time of their check angiogram prior to PCI had developed significant angiographic regression of their CAD and did not require PCI.
Conclusion: On the PCI waiting list there is a high rate of CAD progression necessitating surgical revascularisation. There is also a high incidence of emergency UA admissions. In the current environment with long waits, the rate of death or AMI are low. A policy of proceeding with PCI at the time of the angiogram would prevent emergency admissions and thereby promote efficient bed usage.

P2259 Safety of administration of protamin after coronary angioplasty

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Purpose: To study coronary safety of immediate reversal of heparin with protamin after successful PTCA, as well as puncture complications, time to mobilization, and patient comfort.
Methods: 100 patients with femoral puncture and a successful PTCA were prospectively randomized to protamin reversal and immediate sheath removal or sheath removal after three hours. Exclusion criteria were insulin dependant diabetes, myocardial infarction within the last 14 days and the need for GP IIb/IIIa platelet inhibitors. 34 women and 66 men were included, mean age 64 ± 11, range 42 - 82. When randomized to protamin, the activated clotting time was measured and the dose of protamin was given accordingly. All patients were followed up after 24 hours and 30 days.
Results: 50 patients were randomized to receive protamin. 78 patients had treatment of one vessel, 19 patients two vessels and 2 patients three vessels. Stents were implanted in 91 patients (91%). At six month two vessels were occluded (4%) and seven (14%) had recurrent stenosis in the protamin group, 4% and 10% respectively for the control group. However, four patients had early symptoms in the protamin group and only one in the control group, requiring reintervention. Pseudoaneurims were seen in one patient in the protamin group and two in the controls. Ten patients (20%) in the non-treated group had hematomas of any size, one large and one medium sized. Fifteen patients (30%) in the treated group had hematomas of any size, 1 large and five medium sized. The time to mobilization was significantly shorter for the protamin group, 10 hours vs. 17 hours. The overall patient discomfort from compression, bed rest and groin pain was less in the protamin group.
Conclusion: Reversal of heparin with protamin immediately after PCI improved the patient comfort and the practical handling of the patients having femoral puncture. Howerver, there was a trend toward more cardiac complication and further studies are recommended before this treatment should be used routinely.

P2260 Revisited values of Troponin I for the diagnosis of myocardial infarction after PTCA: results from the prospective French VIGILANCE Registry

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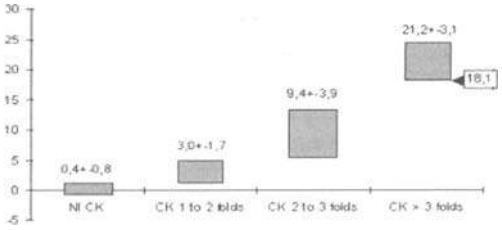
Though troponin rise is now considered by many to be a marker of poorer outcome after PTCA, there is less evidence to this than for post-procedural CK rise.
The aim of the present study was therefore to determine the relationship between CK and troponin post-procedural levels in a population prospectively included in a multicentre registry of patients undergoing placement of a Cordis BxVelocity ® stent. Troponin I and CK were analysed before PTCA and on the morning following the procedure; all measurements were made at a central core laboratory.
191 patients with both normal CK (<170U) and normal Troponin I (<1U) values before PTCA were included in the study.
For the whole group, we observed a rise in CK and Troponin I values after PTCA (Troponin I from 0.1±0.2 to 0.9±2.7 p<.0001, CK from 51.1±29.3 to 80.1±104.4 p<.0001). Troponin I was >= 1U in 32 patients (16.7%), CK was >= 170U in 17 patients (8.9%). There was a significant correlation between CK and Troponin I (r = 0.878, p<0.0001).
Furthermore, when the values for Troponin I were analysed according to CK values (normal, >1 to 2, >2 to 3 and > 3 times the upper limit of normal). Only very high (> 18 U) troponin values corresponded to CK increase above 3 times the upper limit of normal, a threshold considered diagnostic of clinically relevant myocardial damage in most studies.



Troponin values vs CK range.

In conclusion, if CK measurements are replaced by Troponin I measurements after PTCA only the highest values of Troponin I correspond to the threshold used for CK values.

P2261 Does stent design affect platelet activation? Results of the platelet activation in stenting (PAST) study

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Background: Platelet activation induced by coronary artery stenting affects clinical outcomes and may be related to stent design. However, little is known about how platelet activation may be altered by the specific design of a stent.
Methods: Patients (n=53) were randomly assigned to stenting with a closed-cell (NIR, Boston Scientific) or open-cell (TETRA, Guidant) stent. Patients were treated with aspirin and were loaded with 300 mg clopidogrel in the cath lab and received 75 mg daily thereafter. All stents were depolyed at > 12 atm. GPIIb/IIIa inhibitors were not used. Platelet aggregation (5μ mol ADP and 1μg/ml collagen); and flow cytometry (mean fluorescence intensity (MFI)) to multiple platelet receptors and platelet-leukocyte aggregates (CD 151+ 14) were serially determined at baseline, and at 2 hours (2h), 24 hours (24h), 5 days (5d) and 30 days (30d) post procedure.
Results: Stenting was successful in all patients. Markers of platelet activation were less following NIR implantation: 30d ADP aggregation (%) (32.3±6.1 vs 44.5± 18.9, p=.02); 24h CD 31 (136±48 vs. 110±48,p=.04); 24h (104±45 vs 91±31 p=.048) and 30d CD 151 (99±33 vs 81±32, p=.03);24h (93±40 vs. 77±24, p=.018)and 30d CD 151+14 (84±35 vs. 72±31, p=.045); 30d PAC-1 (88±41 vs 72±30, p=.025); and 2h (22±13 vs 18±5, p=.045) and 24h CD 107a (24±12 vs. 17±4, p=.03).
Conclusions: In this randomized prospective trial, platelet activation; indicated by enhanced aggregation and expression of multiple receptors; was greater during the 30 days following implantation of an open-versus a closed-cell stent. Stent-dependent platelet activation may be relevant to the propensity for subacute thrombosis and restenosis associated with a particular stent design.

P2262 Coronary microembolisation – Its role in chronic total coronary occlusions and interventions

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Introduction: After recanalisation and stenting of chronic total coronary occlusions (TCO), a reduced coronary flow velocity reserve (CFVR) and rise in collateral resistance (Rcoll) are frequently observed. Coronary microembolisation may account for these observations.
Methods: In 71 patients (age 64 ± 10 years; 65 men, 6 women) with TCO (duration >4 weeks), PTCA was performed with successful stent implantation in all lesions. Before PTCA viable myocardium was detected by stress echocardiography or nuclear imaging techniques. In order to calculate Rcoll coronary pressure was measured before the first balloon inflation and after PTCA had been completed. In order to determine CFVR coronary Doppler flow velocity was measured after PTCA had been completed. Before and over a period of 24 hours after intervention creatine kinase (CK) and cardiac troponin (cTNI) were monitored.
Results: CFVR was <2.0 in 52% of all patients. A rise in Rcoll was observed in 84% of all patients. The incidence of CK and cTNI elevation above the 99% confidence limit was only 6% of all patients. These patients with CK and cTNI elevation did not show a significant difference of CVFR and rise in Rcoll as compared to patients without CK and cTNI elevation. CVFR or rise in Rcoll did not correlate with CK or cTNI elevation.

Interventional results

	All patients	CK normal	CK elevated	P
Patients (n)	71	67	4	-
Baseline APV (cm/s)	29.0 ± 15.1	29.1 ± 14.9	27.7 ± 20.4	NS
Hyperemic APV (cm/s)	54.0 ± 25.3	54.0 ± 24.7	54.2 ± 39.5	NS
CFVR	2.0 ± 0.6	2.0 ± 0.6	2.0 ± 0.2	NS
FFR	0.84 ± 0.08	0.85 ± 0.07	0.77 ± 0.21	NS
Rcoll before PTCA (mmHg/(cm*s)	9.6 ± 8.7	9.4 ± 8.5	14.0 ± 13.8	NS
Rcoll after PTCA (mmHg/(cm*s)	20.5 ± 17.2	20.5 ± 17.4	21.8 ± 17.8	NS

APV=Average Peak Velocity, CFVR= Coronary Flow Velocity Reserve, FFR=Fractional Flow Reserve, Rcoll=Collateral Resistance.

Conclusion: Coronary microembolisation is not a likely cause for the microvascular dysfunction and changes of collateral function after PTCA of TCO.

PAEDIATRIC CATHETER INTERVENTION

P2263 Is transcatheter closure of ostium secundum atrial septal defect superior to surgery?

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Background: Surgical ASD closure provides excellent results. With the current rise of percutaneous techniques, a comparison is needed.
Aim: To compare percutaneous and surgical closure of ASD.
Patients and methods: Between December 1988 and August 2001 909 consecutive patients underwent ASD closure in our institution. From 4/96 to 08/01, 478 pts underwent percutaneous ASD closure (Group A). Two devices were used: Amplatzer Septal Occluder in 347 pts (72.6%) and CardioSEAL/StarFLEX in 131 pts (27.4%). From 12/88 to 08/01, 443 consecutive pts underwent ostium secundum ASD surgical repair (Group B). There was a slight difference in mean age between the two groups (Group A: 28.6±19.8 yrs vs Group B 21.4±19.25 yrs; p=0.02).
Results: Hospital stay was lower in Group A (3.2±0.9 days vs 10.1±2.6 days; p<0.0001).Total number of complications was higher in Group B (43% vs 11%; p<0.0001) as well as clinically relevant complications (19% vs 3.8%; p:0.002). In Group A major complications included: (a) device embolisation needing surgical retrieval (12 pts; 2.5%); (b) surgical repair of femoral vessels (4 pts; 0.8%); (c) arrhythmias (11 pts; 2.3%); (d) trombus formation on the device (2 pts; 0.4%). In Group B complications included: minor transient complications in 24% of the pts (arrhythmias, respiratory infections, pericardial effusion, anemia, pneumothorax,others); severe transient in 18.3% (arrhytmias, sever bleeding, heart failure, transient complete AV block, cardiac tamponade); severe with sequelae in 3 pts (0.7%) (neurologic, chronic cardiac failure). Transfusion rate was 5%. Surgical drainage for pericardial or pleural effusion or for pneumothorax was needed in 4.5%. Chest reopening for severe bleeding was in 0.5%. Re-operation for patch detachement occurred in 2 pts. No early deaths occurred in both groups. Residual shunt at discharge was trivial and there were no differences between the two groups. Five pts of Group A and 5 pts of Group B were treated for a significant residual shunt after surgical ASD closure.
Costs were higher in Group B (8096±1171 vs 7791±2928 Euro; p=0.04).
Conclusions: Percutaneous ASD closure provides excellent results, with lower complication, no sequelae, shorter hospital stay and reduced costs.

P2264 Amplatzer occluder device in adult patients with secundum atrial septal deffect: a single center experience

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Background: Secundum atrial septal defect (ASD) is a common congenital heart disease in adulthood. Amplatzer septal occluder (ASO) device is one of the most recent devices that have undergone to investigation. However, data from adult population with this device are limited. This study evaluates the immediate and at 6 months outcome of the percutaneous ASDs closure with the ASO-device in an adult population in a single centre experience.
Methods and Results: Between May 1999 and September 2001, 36 adult patients (21 female) with a mean age of 44.6+15.1 years (range 26 to 84) were considered for a percutaneous ASD closure with ASO-device after transesophageal echocardiography (TEE). A coronary angiography was performed in patients older than 40 years or with multiple coronary artery disease risk factors. Clinical evaluation and transthoracic echocardiogram (TTE) were done at 24 hour and at 6 months.ASD diameter on TEE was 14.4+7.2 mm (range 4 to 23 mm). The mean stretched defect diameter measured 19.5+8.4 mm (range 8 to 34 mm) and mean ASO-device size was 19.8+ 8.2 mm (range 8 to 34 mm). ASO-device was implanted successfully in 94.4% (34/36) of patients. A trivial shunt was assessed by TEE examination in 14 patients (38.9%) and residual shunt = 3 mm in one patient who had a very pliable posterior rim. In 2 (5.6%) cases ASO closure failed because the defect was too large. In 3 (8.3%) of the 36 patients an associated coronary artery disease was assessed. A percutaneous transcatheter coronary angioplasty (PTCA) was successfully performed before ASO deployment.
At 6 month 2 (5.6%) of the 36 patients developed a supra-ventricular arrhythmia and needed medical treatment. No shunt was assessed on TTE in the patients in whom a trivial shunt was visible after procedure and a reduction of the bigger residual shunt was shown by TTE examination
Conclusions: 1. TEE examination aloud a good screening of the ASD that may benefit of ASO closure device (However, in 5.6% of cases ASO device can not be implanted because of ASD too large or pliable rims, even after TEE examination). 2. Transcatheter closure of ASDs is a safe and effective alternative to surgical closure in most of the adult patients with excellent immediate and middle-term outcome. 3. Combined PTCA and percutaneous ASD closure are safe and effective. Non-invasive tests to detect myocardium ischemia are advisable in every adult patient who is undergoing percutaneous ASD closure.

P2265 Short and intermediate term results of tanscatheter closure of atrial septal defect with Amplatzer septal occluder

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Aim.This study was conducted to evaluate the short and intermediate-term results of transcatheter closure of atrial septal defect (ASD) with the Amplatzer septal occluder.
Material and Methods: During a 3 years period, between January 1999 and December 2001, 117 patients underwent attempted transcatheter closure of ASD using the Amplatzer septal occluder in this institution. After hemodynamic studies, an AGA balloon sizing catheter was used to measure the stretched diameters of the defect. A sizing plate was also used to evaluate the accuracy of the measurment of the sizing catheter. All patients underwent general anesthesia with transesophageal echocardiographic monitoring of the procedure. The diameter of the device used was equal to or slightly larger than the stretched diameter if the stretched diameter was < 20 mm. An increment of 2 mm of the stretched diameter was selected as the size of the device, if the stretched diameter > 20 mm.
Results: The Amplatzer device was deployed in 114 patients. In the initial period of the study, the procedure was abandoned because of stretched diameter of the defect > 30 mm in 3 patients. Of the 114 patients, 35 were male, 79 females with ages ranging from 2.5 to 66 years. The mean stretched diameter measured with balloon catheter and sizing plate were 17.3 + 5.2 mm (ranging from 6.2 to 32.4 mm) and 17.6 + 5.6 mm, respectively. Deficiency of anterior superior rim (< 2mm) was found in 58 patients. Seven had multiple fenestrated ASD. An aneurysm of the atrial septum was found in 8. Only one device was deployed in all patients except one who had implantation of two devices. One patient complicated with compete atrioventricular block which recovered 3 days later. Two had small-to moderate amount of pericardial effusion after diagnostic catheterization and angiogram, which subsided in the 2 patients in one month follow-up. All patients received aspirin for 6 months. Echocardiography at 1 day, 3 months, 6 months & 12 months follow-up showed residual shunt in 21/114 (18%), 5/108 (5%), 2/86 (2%), and 2/74 (3%), respectively. The two patients who had residual shunt 12 months after ASD closure had multiple perforated defects. One had several episodes of migraine during follow-up.
Conclusion: Amplatzer septal occluder is safe and effective in the closure of ASD. Deficiency of anterior superior rim did not render difficulties in ASD closure.

P2266 Interventional closure of patent foramen ovale with the Amplatzer PFO occluder: complications and follow-up results in 126 patients

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Purpose: Patients with paradoxical embolism through a patent foramen ovale (PFO) are at risk to suffer from recurrent embolic events. Transcatheter PFO closure has been proposed to prevent recurrent paradoxical embolism. We are reporting our experience using the Amplatzer device.
Methods: Since 8/1994 catheter PFO closure was performed in our center in 535 adult patients. In 126 cases we implanted an Amplatzer PFO Occluder. The mean age of these patients was 49 ± 12 years (range 22- 76 years). In these patients 171 embolic events had occurred before closure (average 1.4 per patient). The defect size (stretched diameter) ranged from 3 to 21 mm (mean 9 ± 3).
Results: The implantation of the device was successful in all patients. The procedure was performed in local anesthesia in 113/126 patients. The mean procedure duration was 34 ± 16 minutes (mean fluoroscopy time 5.3 ± 3.9 min). Patients were discharged after a hospital stay of 0.8 ± 0.4 days. An initial residual shunt could be detected in 39 patients (transesophageal contrast echocardiography). In their last follow up 2 patients still had a small residual shunt. As acute complication occurred one device perforation after 24 hours (surgery uneventful). During follow-up (0.5 to 26 months) the following complications occurred: Recurrent embolic event: n=1, paroxysmal atrial fibrillation: n=5 (cardioversion and medical treatment successful in all of them), on- device thrombus formation n=2.
Conclusion: Transcatheter PFO closure with the Amplatzer PFO occluder is a safe procedure. Midterm results show an effective prevention of recurrent embolic events. Randomized trials are necessary to show long- term prevention.

P2267 Percutanous closure of atrial septal defects in patients with severe pulmonary hypertension – Follow-up results in 48 consecutive patients

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Purpose: We report our experience with the transcatheter closure of atrial septal defects (ASD) in 48 patients with severe pulmonary hypertension (Psyst>50 mmHg).
Methods: Since 8/1992 catheter closure of an ASD was performed in our center in 361 adult patients. In 48/361 patients the systolic pulmonary artery pressure was elevated above 50 mmHg. The mean age was 65±10 years. The stretched diameter of the defects ranged from 13 to 34 mm (20±6), the systolic pulmonary artery pressure ranged from 50 to 110 mmHg (63±14). We used 8 different devices.
Results: The implantation was successful in all 48 patients. The mean procedure time was 56 ±25 minutes (fluoroscopy time 11±9 minutes). Mean hospital stay was 1.4 ± 1.1 days. As complications occurred: Embolisation n=1 (surgery uneventful), pericardial effusion n=1, thrombus n=1, atrial fibrillation n=4. Transesophageal echocardiograpy showed a complete closure in the last follow up in 39 patients. The Qp:Qs ratio decreased from 2.1 ±0.7 before closure to 1.0 ±0.3 after 6 months ($p<0,001$).The mean pulmonary artery pressure decreased from 36 ±9 mmHg to 28 ±8 mmHg ($p<0,001$). The right ventricular diastolic diameter (M-Mode) was reduced from 44 ±6 to 37 ±7 mm ($p<0,05$).
Conclusion: Transcatheter closure of ASD is a safe procedure in elderly patients with pulmonary hypertension. It leads to a significant decrease of pulmonary artery pressure and right ventricular dilatation.

FETAL CARDIOLOGY

P2268 Fetoscopic cardiac interventions in fetal sheep carry a low risk for the occurrence of brain damage detectable following completion of gestation

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Introduction: Open fetal surgery has resulted in considerable neurological damage in human fetuses. Alternatively, minimally invasive fetoscopic approaches that avoid maternal laparotomy and hysterotomy are being developed in sheep. The purpose of this pathohistological study was to assess any discernable damage from fetoscopic cardiac interventions in newborn lambs.
Methods: 12 ewes continued gestation following fetoscopic fetal thoracotomy for cardiac pacing lead insertion (n=8) or fetoscopic fetal cardiac catheterization (n=4) between 92-109 days of gestation (term = 145 days). At term, 10 of the 12 operated fetuses, and 9 unoperated siblings were delivered. The 19 newborn sheep were examined for neurological deficits presenting as movement disorders or the inability to establish a normal feeding pattern. Two of the 12 operated fetuses died early after the procedure yet the ewes continued gestation. At term, life twin and triplet siblings, respectively, were delivered and available for brain studies; the dead fetuses, however, were too mummified to be studied. All brains were fixated in formalin. Following sectioning and mounting, H.E., Klüver-Barreira, and Van Gieson stains were performed. In addition, immunohistochemical staining was performed with KiM1P-, LCA-, and GFAP-antigens. All brains were examined for bleeding complications, embolic events, infarctions as well as acute inflammatory tissue reactions or abnormal cortical maturation.
Results: In all but one prenatally operated lamb (and its unoperated sibling), minimally invasive fetoscopic cardiac interventions did not result in any discernible changes to the brain by the various staining methods. In none of the brains studied, hemorrhages, embolic events, inflammatory tissue reactions or abnormal cortical maturation were observed. In the two affected lambs, chronical cortical frontal lobe infarction (Stage III), compatible with an unobserved period of maternal hypotension, was observed. Despite these changes, the two lambs exhibited normal movements, feeding patterns, and social interactions during their neonatal period.
Conclusions: Fetoscopic cardiac interventions in fetal sheep carry a low risk for the occurrence of brain damage that can be detected following completion of gestation. This safety is encouraging for the clinical introduction of some of these minimally invasive procedures in the near future.

P2269 Intraamniotic fetal echo in sheep permits imaging during cardiac interventions and in fetuses in whom other imaging methods fail

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Introduction: During fetoscopic cardiac interventions intraesophageal placement of intravascular ultrasound catheters for fetal hemodynamic monitoring may result in esophageal injury in very small fetuses. Moreover, conventional fetal cardiac imaging by the transvaginal or transabdominal routes may be impossible in some high-risk pregnancies. Therefore, the purpose of our study in sheep was to assess the potential of a 10-F phased-array intravascular ultrasound catheter for intraamniotic fetal echocardiography.
Methods: The catheter was percutaneously inserted into the amniotic cavity of 7 pregnant ewes between 78-98 days of gestation. We assessed the feasibility of imaging the fetal heart by 2-dimenstional as well as pulsed and color Doppler echocardiography. Following intraamniotic imaging, a small fetoscope was inserted into the amniotic cavity in order to assess any injury to intraamniotic contents from the procedure.
Results: The intraamniotic imaging approach permitted high-quality two-dimensional imaging of the fetal heart as well as multimodal Doppler assessment of fetal cardiovascular flows within 10 minutes following intraamniotic catheter insertion in all but one fetal sheep. In the fetal sheep in that imaging was inadequate, the image quality was impaired by beam scattering from the spine. In all fetuses, fetoscopic examination of intraamniotic contents after intraamniotic imaging was finished did not display any injury to intraamniotic contents. In one fetus, intraamniotic ultrasound imaging was instrumental for defining the exact incision site for fetal thoracotomy in order to insert a pacing lead.
Conclusions: The intraamniotic imaging approach may provide an effective alternative in the human for monitoring of fetoscopic cardiac interventions, and for assessment of fetal cardiac anatomy and hemodynamics in high-risk pregnancies when sufficient images cannot be obtained by conventional routes.

P2270 Improved assessment of fetal cardiac function using Doppler tissue imaging and long axis function

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Background: Assessment of gestational changes in fetal cardiac function has been held back by available methodologies and the interpretation of changes confounded by the gestational increase in ventricular preload. Fetal ejection fraction is unchanged throughout the second half of pregnancy and poorly reflects the known maturational changes in the myocardium and improved calcium handling. Assessment of diastolic ventricular function using inflow velocities is confounded by increasing preload, with the normally reversed early to late inflow ratio precluding its use as an indicator of diastolic dysfunction.
Aim: To examine the feasibility of assessing fetal free wall myocardial function at different gestational ages using its long axis amplitude of motion and to compare it with inflow velocities.
Methods: We examined 63 fetuses; 23 (20-23 weeks), 8 (24-27 weeks), 12 (28-31 weeks), 11 (32-35 weeks) and 9 (36-39 weeks) using long axis amplitude (M-mode) and shortening & lengthening velocities (Doppler Tissue Imaging, DTI).
Results: RV and LV systolic velocities correlated with the progressive increase in the free wall amplitude of motion with increasing gestation, RV: R=0.59, $p<0.0001$; LV: R=0.33, $p<0.01$. This was associated with a progressive gestational increase in outflow tract velocities, RV p=0.00007 and LV p=0.0004. Early (p=0.009) and late ($p<0.03$) diastolic free wall velocities increased with age along with the corresponding increase in trans-tricuspid flow velocities ($p<0.00001$ and p=0.04) but late diastolic left free wall velocities increased (p=0.004) in the absence of increased trans-mitral flow (p=0.44).
Conclusion: DTI and long axis studies confirm that fetal systolic and diastolic function improves significantly throughout gestation. These findings form the basis for normal fetal ventricular data that can be applied in disease states.

RISKS OF CARDIAC SURGERY

P2271 Reoperation for mechanical prosthetic heart valve thrombosis. A single center study about 136 patients

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Prosthetic heart valve thrombosis (PHVT) is a potentially fatal complication of heart valve replacement surgery. The purpose of this report is to present experience of a single center about 136 consecutive patients operated on between 1978 and 2001.
The diagnosis of PHVT was established mainly by fluoroscopy and/or echocardiography. Obstructed valves consisted of 82 bileaflet; 47 tilting disc and 7 ball cage valves. Thrombosis concerned 94 mitral valves, 41 aortic valves, 1 mitro-tricuspid valve.
The mean interval between the initial surgery and thrombosis was 7.4 ± 66 years (1 day to 28 years), 37 pts underwent preoperative medical therapy with incomplete or no results (21 fibrinolysis, 16 heparin therapy).
Operative procedure included valve replacement in 101 cases and declotting in 30 cases.
Overall, full success was observed in 121/136 pts (89%). The perioperative mortality rate was 10.3% (14 patients) particularly NYHA class III or IV patients. One documented perioperative embolic event occurred. Finally PHVT recured in 10 patients (7.4%) during follow-up.
It is concluded that nowadays for most PHVT early reoperation is effective and safe, particularly in patients who are in stable condition preoperatively.

P2272 Mechanical prosthetic heart valve thrombosis: fibrinolysis or surgery? A single center study about 253 patients

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Prosthetic heart valve thrombosis (PHVT) is a serious complication of mechanical valve replacement. Surgery is the favoured treatment but fibrinolysis has been proposed as an attractive alternative. We report a larger single center series in order to better define efficacy and safety of these 2 options.
From 1978 to 2001, 253 cases of PHVT were managed in our institution either by surgery (n = 136) or by fibrinolysis (n = 127). Obstructed valves were 169 mitral, 84 aortic and 4 tricuspid, 161 bileaflet, 95 tilting disc and 7 ball cage valves. 37 patients underwent preoperative medical therapy with incomplete or absent results (21 fibrinolysis, 16 heparin therapy). Main results are summarized on the table.

Results	Surgery	Fibrinolysis	p
Full success	88.9% (120)	70.9% (90)	< 0.01
Incomplete	0 (0)	17.3% (22)	< 0.01
Failure	0 (0)	11.8% (15)	NS
Haemorrhage	0.7% (1)	3.9% (5)	0.08
Embolism	0.7% (1)	15.0% (19)	< 0.01
Death	10.4% (14)	11.8% (15)	NS
Total complications	11.1% (16)	24.4% (31)	< 0.01
Reccurences	7.4% (10)	18.9% (24)	< 0.01

In conclusion, nowadays, in patients with PHVT, surgery is the treatment of choice. However, fibrinolysis may be indicated for selected patients right sided PHVT, critically ill patients at high risk with surgery.

P2273 Perioperative myocardial infarction following coronary bypass: short and long-term follow-up

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Perioperative myocardial infarction (PMI) is a major complication following coronary artery bypass graft. Clinical significance of PMI is controversial and has not been sufficiently studied. The aim of the present study was to assess the short and long-term follow-up of a large cohort of patients with PMI.
Methods: 702 patients who had undergone coronary bypass grafting between 1993 and 2000 were retrospectively studied. PMI was defined when new pathological Q waves and CK-MB elevation were demonstrated after surgery. Patients were divided into two groups: 97 patients (13,8%) with PMI (group A) and 605 patients without PMI (group B).
Results: Baseline demographic and clinical characteristics were similar between the two groups. In-hospital mortality was higher in group A than in group B (14% vs 4%, RR:1,39 95% CI 1.1 to 1.8; $p<0.001$). Also hospital mean stay was longer in group A compared with group B (25 days, SD 14 vs 13 days, SD 5; $p<0.001$) At 53.6 months (SD 25.3, range 9-100 months) follow-up more patients in group A than in group B had cardiac events: unstable angina (25% vs 11%, RR: 1,18 95% CI 1.1 to 1.4, p=0.001), congestive heart failure (32% vs 8%, RR:1,43 95% CI 1.2 to 1.8, $p<0.001$), and repeated revascularization procedures (23% vs 9%, RR:1,19 95% CI 1.1 to 1.4, p=0.001). The 8-year event-free survival rate (Kaplan-Meier) was lower in the group A (76 months, 95% CI; 68 to 84 months) than group B (85.5 months, 95% CI; 82 to 87 months), p=0,02. However, after excluding in-hospital deaths, the long-term mortality between the two groups was not significantly different (14% in group A vs 12% in group B).
Conclusions: PMI was associated with both a high in-hospital morbidity and mortality. However, a high number of long-term cardiac events in patients with PMI was not associated with a worse long term survival than those without PMI.

P2274 Relationship between body mass index and postoperative complications after cardiac surgery

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Background Among other preoperative parameters, severe obesity and cachexia are regarded as substantial risk factors for postoperative complications. However, the exact relationship between body mass index (BMI) and postoperative risk has not yet been defined.
Methods We retrospectively investigated consecutive patients (n=20,680) who underwent cardiac surgery between 1990 and 2000 in our institution. BMI, age, gender and type of surgery were used as covariates in a logistic regression model. The adjusted odds ratios (OR) for increases in BMI of 1 kg/m^2 were calculated for three endpoints, re-intubation, early infection and 30-day mortality.
Results With increased BMI the OR for re-intubation, infection and 30-day mortality continuously decreased. The BMI with the lowest OR was between 25 and 35, between 25 and 27 and between 33 and 35 kg/m^2, respectively. The OR for postoperative complications, except for infections were significantly higher in cachectic patients compared with obese or severely obese patients (table).

Odds ratios for postop. complications

BMI (kg/m^2)	OR and CI for re-intubation	OR and CI for infection	OR and CI for 30-day mortality
<20	2.18 (1.83-3.11)	1.66 (1.29-2.14)	1.6 (1.17-2.18)
30 - 40	1.08 (0.87-1.33)	1.34 (1.19-1.51)	0.72 (0.59-0.88)
>40	1.05 (0.26-4.34)	3.91 (2.24-6.82)	0.7 (0.17-2.87)

OR: odds ratio, CI: confidence interval

Conclusion There is a non-linear relationship between BMI and risk for postoperative complications after cardiac surgery. The slightly underweight and cachectic patients were at higher risk after cardiac surgery than obese or even severely obese patients. A preoperative focus on avoiding and/or reversing cachexia may be more efficacious than reducing obesity in decreasing the overall risk associated with heart surgery.

P2275 Low high density lipoprotein cholesterol predicts mortality in long-term follow-up after coronary artery bypass surgery

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Background: Low HDL-c is an independent predictor of coronary heart disease (CHD) comparable or even stronger than high LDL-c. However the influence of low HDL-c following coronary artery bypass graft (CABG) is less known.
Objectives: To assess the influence of low HDL-c on mortality in patients submitted to CABG, followed for a mean period of 6.3 years.
Material and Methods: We studied 165 patients of both gender, and divided then into two groups: I, HDL-c <=35 mg/dl (n = 101),and II, HDL-c > 35 mg/dl (n=64). The CABG occurred between 1994 and 1996.
Results: Group I and II were comparable (p-ns) as far as gender (75.5% males vs 62.5%), age (65.4 ±8.4 vs 67.4 ±9.2) years, diabetes (40.5% vs 34.3%), hypertension (66.1% vs 70.3%), hipercholesterolemia (61.2% vs 59.3%), family history of CHD (61.3% vs 78.1%), previous myocardial infarction (50.4% vs 51.5%), smoking (39.5% vs 35.5%) sedentarism (42.5% vs 39.0%) and body mass index (BMI 29.6% vs 18.7%). The extent of CAD in both groups was similar: single vessel disease (5.94% vs 9.37%), and multiple vessel disease (94.0% vs 90.6%). The number of graft employed was also similar (1.60 ±0.91 vs 1.40 ±1.0). As far as lipids and glucose, only HDL-c was different between the groups (Table - Lipid profile in mg/dl). At the follow up, there were 21 (20.7%) deaths in group I, but only 4 (6.25%) deaths, in group II (p = 0,01, chi square). When adjusted for cholesterol, sedentarism, B.M.I., diabetes, triglycerides, hypertension, family history of CHD, previous myocardial infarction, smoking, extent of CAD, and number of grafts, HDL-c emerged as an independent predictor of cardiovascular deaths (p value = 0,01), by logistic regression model.

Lipid profile

Mean	Group I	Group II	Mean	Group I	Group II
Glycemia	150.2	119.0	Trygliceride	245.1	152.3
Cholesterol	225.1	231.7	LDL	148.0	155.7
HDL	28.1	44.8	VLDL	58.7	33.5

Conclusion: Low HDL-c level predicted significantly greater cardiovascular mortality after CABG in men and women. Whether its correction would improve outcome needes further investigation.

P2276 Role of myocardial revascularization in patients undergoing high-risk vascular surgery

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Cardiac events are the major cause of mortality after vascular surgery. Determination of high-risk patients is a major goal for clinicians before surgery; clinical evaluation and non-invasive techniques can help for the determination of risk, but up it has not yet been establisehd whether revascularization is of value, even when feasible.
234 consecutive patients (pts) (65±10 years, 91% males) undergoing staged abdominal aortic surgery were retrospectively studied. Three groups were defined according to clinical data. Group A (n=162): pts without ischemia based on clinical history, and/or negative test (stress echocardiography or treadmill or nuclide myocardial scintigraphy); group B (n=27): pts with ischemia: high ACC/AHA score, and/or positive stress, leading to coronary angiogram (CA) and revascularization (20 pts with PTCA, 7 with coronary bypass surgery); group C (n=45): pts with ischemia, with or without CA, and without revascularization.
Vascular surgery was performed at least 14 days after revascularization; all patients with stents (19) were treated by aspirin and ticlopidine or clopidogrel for at least 21 days.
Thirteen (5.5%) Major Cardiac Events (MACE) (myocardial infarction, cardiac insufficiency, unstable angina, ventricular arrythmia) occurred after vascular surgery; no patient died. The rates of MACE after vascular surgery were significantly different between groups: A: 3.1%, B: 7.4%, C: 13.3%, p<0.05. One myocardial infarction occurred after coronary revascularization, and the total rate of MACE for group B (coronary revascularization and vascular surgery MACE) increased to 11.1%, non significantly different from group C.
The risk of MACE after vascular surgery was correlated with Eagle Score, ejection fraction and number of diseased vessels (NDV) at CA (from groups A and C with CA, and group B after revascularization). Only NDV was predictive of MACE on multivariate analysis.
The theoretical risk of MACE in group B (if they had not been revascularized) according to the relationship between MACE and NDV, would be 6 patients (22.2%) instead of 3. Compared to group C (13.3%), the difference is significant.
In conclusion: the risk of major cardiac events after aortic surgery is currently highly correlated with the extent of coronary disease; the risk associated with pre-surgery revascularization is low, and this strategy allows a dramatic decrease in the occurrence of MACE.

P2277 CABG in women: higher risk?

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Background: Popular risk scores (Euro Score, Parsonnet) indicate that CABG in women carries higher risk than in men. The reason for this wellknwon finding is not quite clear.
Methods and Patients: 2593 CABG patients operated in 1980, 1990, 1995, 1998, 1999 were reviewed and analysed for gender-associated risk of surgery.
Results: Overall early mortality was 1.9%; 3.8% for women and 1.5% for men (p=0.001). Compared with males, females were older (64.2 years vs 58.3; p=0.01), more symptomatic (74% CCS IV-V vs 50%; p=0.001), preoperative iv heparin was more frequent (31% vs 20%; p=0.01), surgery was more frequently urgent (37% vs 27%; p=0.001), females were more likely to be hypertensive (67% vs. 51%; p=0.001), and diabetic (21% vs 16%; p=0.01) No significant sex-related differences weree found for the incidence of left main stenosis, number of diseased vessels, ejection fraction, use of IMA, and duration of cardiopulmonary bypass. Multivariate analysis revealed that age, poor ejection fraction, intensity of angina, and prior PTCA were indipendent risk factors for early mortality after CABG. There was only a weak trend for female sex as an independent factor (p=0.07).
Conclusions: There is at most only a weak association between female gender and early mortality after isolated CABG. In the multivariate analysis, female sex is a less important risk factor than age, poor ejection fraction, intensity of angina and prior PTCA.

CARDIAC REHABILLITATION

P2278 Respiratory capacity and autonomic modulation in heart transplant patients

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Background: In a previous study of heart transplant patients we showed an increase in autonomic modulation towards the native sinus node (NSN) after heart transplantation (HTX), while the donor heart remained extrinsically denervated. This study focussed on the influence of the restoration of autonomic modulation on respiratory capacity.
Methods: 10 HTX patients were enrolled in this study. 5 patients were involved in a voluntary exercise program at home (>3 hours/week) and 5 were used as a control group. Intracardiac electrogram measurements of the NSN started from a few weeks after HTX and then monthly up to 1 year. A progressive climbing exertion test till exhaustion was performed to determine maximal oxygen consumption and maximal power level at 3, 7 and 12 months after HTX. ECG was recorded continuously. Heart rate variability (HRV) was computed on the electrogram of the NSN and the ECG of the exercise test at peak exercise level and low (LF) and high frequency power (HF) determined.
Results: Intracardiac HRV of the NSN showed a progressive increase in LF and HF ($p<0.05$ at 7 months) in all patients. At 1 year the increase in LF and HF levelled off. There was no significant increase in peak oxygen consumption, maximum workload or in any HRV parameter measured at maximum workload up to 1 year after HTX. A minor increase was observed after 7 months in most indices but this evolution did not progress. No difference in evolution was observed between the active group and the sedentary group.
There was a significant difference between the active group and the sedentary group in maximum power (95±27 W vs 56±14 W;$p<0.001$), max HR during exercise (147±26 bpm vs 124±21 bpm;$p<0.05$) and VO2 (1394±329 ml/min vs 829±182 ml/min;$p<0.001$). There was no difference in rest HR or peak exercise HRV indices.
Conclusion: Training causes a larger exercise tolerance, which is beneficial for the quality of life after HTX, but does not stimulate the restoration of autonomic modulation towards the NSN.

P2279 Exercise recommendation for patients with coronary artery disease – Risk of catecholamine overload

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Introduction: Exercise training for patients with coronary artery disease (CAD) is recommended in a wide range between 40-85% of maximum functional capacity (MFC) or 55-90% of maximal heart rate (American Heart Association, American College of Sportsmedicine). During exercise high levels of catecholamines and metabolic acidosis could induce arryhthmias and cardiac ischemia. But catecholamines have never been determined in CAD during exercise in the upper range of recommended intensities.
Methods: In 11 CAD (age 58 ± 8 years, BMI 26.1 ± 4.0 kg/m^2, NYHA I n=7, II n=4) we tested the maximal functional capacity, norepinephrine (NE), epinephrine (E) and blood lactate (Lac) kinetics in a symptom limited incremental ergometer test. Related to exercise recommendation, the kinetics of NE, E and Lac were determined in two 30 min constant load tests in randomized order: one was performed at the anaerobic lactate threshold (CTAT), a second was performed 10% above the individual threshold intensity (CT+10%).
Results: Maximal values at MFC (end of incremental tests), of CTAT and of CT+10% are shown in the table. In CTAT the anaerobic threshold (63 ± 7% of MFC) represented the mean range of recommended exercise intensity for CAD (40-85%) and could validated as steady-state-intensity because Lac and NE concentrations remained constant after the initial increase. In all patients CT+10% (71 ± 7% of MFC) lead to a continous rise in Lac, to a NE overload and to earlier exhaustion, although the intenisties were in the recommended range.

	Work w	NE nmol/l	E nmol/l	Lac mmol/l	HR b/min	VO2 ml/min
MFC	141±54	11.7±5.1	1.6±1.4	5.7±1.9	138±28	1766±532
CTAT	88±35	8.3±3.5	0.8±0.7	3.3±1.4	117±23	1306±402
CT+10%	100±38*	13.9±6.9*	1.5±1.7	5.8±1.9*	129±29*	1589±465*

Mean values ± SD at MFC, CTAT and CT+10% (CTAT vs. CT+10% * = $p<0.01$)

Conclusion: In the upper range of recommended intensity for CAD norepinephrine and lactate were higher during endurance exercise than at MFC in incremental tests. Endurance exercise with intensities >70% of MFC could overload the cardiac patient and increase the risk of arryhthmias and cardiac ischemia. Therefore, endurance exercise should be performed below 70% of MFC or below 85% of maximum HR, respectively, whereas higher intensities should apply to interval exercise.

P2280 Beta-blocking agents and erectile dysfunction after acute myocardial infarction: guilty or innocent?

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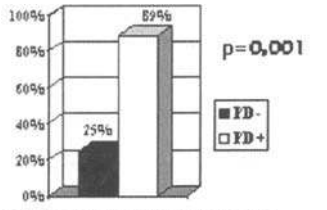
Background: With the use of beta blocking agents in hypertensive patients, incidence of erectile dysfunction (ED) ranges from 5 to 15%. Conclusive data regarding the incidence of ED is not available neither that on the existence of a correlation with the use of the drug during the post-acute myocardial infarction (AMI) period. We analyzed the incidence of ED in acute myocardial infarction patients and investigated possible predictors of ED after AMI.
Methods: We have evaluated male patients that, prior to the AMI, had an active sexual life, without ED. We have evaluated the influence of the fear of starting sexual intercourse again after the event, age, diabetes, arterial hypertension, smoking, dyslipidemia, presence of psychiatric disorders (PD) and the use of drugs (beta blockers, platelet anti-aggregants, ACE inhibitors and statins)in the occurrence of ED until the sixth month after the AMI.
Results: From September/2000 to March/2001 we surveyed 37 male patients with AMI. Ninety-one percent of the patients reported resumption of sexual activity after AMI. Prior to their illness, the mean frequency of sexual activity was 8 times a month. The mean frequency was reduced to 5 times a month ($p<0.001$). After 6 months, 15 (40%)presented with ED. Patients with PD presented with a more pronounced ED than those without PD (Picture 1). We did not detect a difference with regard to the incidence of ED among the groups with or without beta blockers (35.7 x 55.5%, p=0.4). The remaining variables did not correlate with ED.



Erectile Dysfunctions incidence, regarding PD absent (-) or present (+)

Conclusions: After AMI there is a high incidence of ED. Presence of PD was related to this higher incidence of ED. The use of beta-blocking agents and the other analyzed variables are not correlated to the presence of ED.

P2281 Psychological assessments for cardiac rehabilitation

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Purpose: To investigate changes in psychological and quality of life scores before and after a cardiac rehabilitation (CR) program using three simple questionnaires and to test the sensitivity of these instruments.
Methods: Retrospective study of 1403 patients who entered CR over 51 months in a community-based, hospital-linked CR center. Patients completed questionnaires before and after their exercise-based program - Hospital Anxiety and Depression scale, WONCA/COOP charts and an analogue score of wellbeing.
Results: The three instruments took about 4 minutes in total to complete. There were highly significant reductions in mean anxiety score - 6.04 to 4.67 ($p<0.001$, 95% CI -1.52 to -1.16) and depression from 4.00 to 2.52 ($p<0.001$, 95% CI -1.62 to -1.29). The mean analogue of wellbeing score improved from 7.09 to 8.19 ($p<0.001$, 95% CI 0.97 to 1.22). There were highly significant improvements in five of the six WONCA domains. There were significant correlations between improvements in scores from all instruments. The sensitivity indices were in the "good" range for changes in the WONCA physical fitness domain and subjective wellbeing score and in the "moderate" range for changes in depression, well-being and WONCA overall health. Initial physical fitness was significantly correlated with all psychometric scores except anxiety and WONCA feelings, but improvements in fitness were not correlated with improvements of any of the psychometric scores.
Conclusion: The instruments described were quick to administer and showed sensitivities to change superior to those which have been reported for other questionnaires. We believe them to be practical tools for use in CR units.

P2282 Remodelling in patients with left ventricular dysfunction after coronary artery by-pass graft surgery

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Although progressive left ventricular (LV)dilation is associated with adverse cardiovascular events, remodeling after coronary artery by-pass graft surgery (CABG)has still to be investigated. We studied 140 consecutive patients (120 males; mean age 65±9 yrs)with moderate to severe LV dysfunction (EF<=35%), who underwent serial 2-D echocardiography at 12±9 days and at 6 months after surgical revascularization. During this study period, both end-diastolic volume index (EDVi, from 85±23 to 86±26 ml/m^2, NS) and EF (from 28%±6% to 32%±9%, p<0.0001)increased, whereas wall motion score index (WMSI) decreased (from 2.19±0.5 to 2.04±0.4, p<0.0001). At 6 months, a subset of 41 patients (30%) showed a >=15% LV dilation (severe dilation), while EDVi decreased more than 5% in 47 patients (33%), it remained unchanged in 29 (21%), and increased from 5% to 14% in 23 (16%). Independent predictors of severe LV dilation were a relatively small EDVi early after CABG (OR 0.94, CI 0.92-0.97, p=0.0008), a relatively high WMSI (OR 5.99, CI 1.05-34.2, p<0.05) and a partial revascularization procedure (OR 1.8, CI 1.2-2.6, p<0.001). In addition, at 1 year follow-up, major cardiovascular events (including death, heart failure, acute myocardial infarction, pulmonary embolism, need of repeated coronary artery revascularization) were higher in patients with severe LV dilation than those without (34% vs 16%, p<0.01). In conclusion, over a period of 6 months, surgical revascularization does not appear to prevent LV remodeling in a sizeable number of patients with moderate to severe LV dysfunction. Patients with not significantly enlarged ventricular volume early after CABG but with extensive asynergy and partial revascularization are at higher risk for progressive LV dilation, which may significantly affect prognosis.

P2283 Preparing patients for rehabilitation: fast remission of pleural effusions following cardiosurgery with spironolactone

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Pleural effusions represent a frequent complication following cardiosurgery. Fast relief of respiratory symptoms is essential for the efficiency of exercise training during phase I rehabilitation programs. We studied the effect of combined spironolactone + furosemide compared to the usual scheme of furosemide only in the treatment of these effusions. 120 patients (67 following bypass surgery, 50 valvular replacement, 3 following bypass surgery + valvular replacement) out of 483 pts. included in phase I rehabilitation between jan 2000-dec 2001 presented with pleural effusion (right, left or bilateral) at 7-10 days postoperatively. All patients were in stable clinical condition and did not require thoracentesis at admission. Patients with left ventricular ejection fractions <40% were excluded. Cardioactive medication was kept in all cases. The patients were randomly divided into 2 groups: 57 pts. were given spironolactone+furosemide (gr.1), 63 pts furosemide only (gr.2). All medication was oral. In gr.1 mean age was 56,98±11,29 years (20;77), 46 M, 11F, 26 following bypass surgery, 28 after valvular replacement, 3 after both procedures.The mean dosis of spironolactone was 72,37±25,74 mg/daily+furosemide 30,88±13,53 mg/daily. In gr.2 mean age was 60,51 ±8,51 years (39:74) 39 M, 24 F, 41 following bypass surgery, 22 after valvular replacement. Mean dosis of furosemide was 28,73±13,74 mg/daily. **Results:** Complete remission was significant in gr.1, 38 cases (66,7%), compared to 16 cases in gr.2 (25,4%) p<0,01. Duration of treatment to complete remission was significantly shorter in gr.1, 7,84 ± 3,57 days compared to 9,98 ± 4,67 days in gr.2 (p<0,01). K supplements were needed in significantly fewer patients in gr.1, 34 (59,6%) compared to 59(93,7%) patients in gr.2 (p<0,001). Complications: 3 cases needed thoracentesis due to massive accumulation of pleural fluid, nonresponsive to diuretic therapy in each group, 1 case required continous tube drainage due to infection in gr.2. **Conclusion:** Association of spironolactone to furosemide in the treatment of pleural effusions following cardiosurgery appears to have a spectacular effect leading to quick remissions. This result can not be exclusively related to additive diuretic effects, although sequential blockade of the nephrone has to be taken into consideration. The antiproliferative and membrane-modifying effect of canrenone may explain our results. The nature of the fluid (transudate or exudate) could explain differences in duration of remission.

P2284 Neurohormonal abnormalities and the excise trainging effects in cachexic patients with acute myocardial infarction

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Exercise training after acute myocardial infarction is widely accepted because of its beneficial effects. This study was designed 1) to evaluate whether cachexic and overweight patients with acute myocardial infarction (AMI) are affected differently when they undergo exercise training, and 2) to evaluate whether differences in body weight influence the effects of exercise training in AMI patients.

Methods: 192 patients who performed cardiopulmonary exercise training after AMI were enrolled in this study (average 60.4 years). All patients performed regular exercise training for 6 months. Cardiopulmonary exercise testing was performed at 1 month (1mo), 3 months (3mo), and 6 months (6mo) after the onset of AMI. Plasma concentrations of noradrenaline (NA), brain natriuretic peptide (BNP), and tumor necrosis factor-soluble receptors (TNFR-I and TNFR-II) were measured. Patients were divided by the obesity index (OI=body mass index/22) into three groups (body wasting (BW n=31) OI<0.95, normal body weight (NB n=114) 96<OI<110, overweight (OB n=47) OI>111).

Results: Ejection fraction (EF), NA, BNP, TNF R-I and TNF R-II values were similar in the three groups before exercise training.

There were no relationships between peak VO2 and the levels of TNFR-I (r=0.33) and TNFR-II (r=0.33). The peak VO2 was related to TNFR-I (r=0.54, p<0.0001) and TNFR-II (r=-0.56, p<0.001) in the body wasting group, but not in the overweight group. Peak VO2 was related to the level of BNP in both the body wasting group (r=0.61, p=0.003) and overweight group (p=0.49, p=0.009). While peak VO2 showed no significant change from 1mo to 3mo, it increased significantly from 3mo to 6mo (22.6±5.4 to 25.0±6.4 ml/min/kg) in the BW group. In both the NB and OB groups, peak VO2 improved from 1 mo to 3 mo (23.9±4.5 to 25.8±5.8, 22.3±4.1 to 24.4±5.0), but not from 3mo to 6mo. The change in peak VO2 from 1mo to 3mo was lower in the BW group than in the NB and OW groups.

Conclusion: While the level of TNF receptor was similar in all three groups, it was related to the exercise capacity in only the body wasting group. In these patients, exercise training should be continued for at least 6 months. This result suggests that cytokines may be important factors for anticipating exercise tolerance in AMI patients with body wasting due to loss of skeletal muscle volume.

P2285 The effect of short-term endurance training on the insulin resistance indicators in patients with arterial hypertension rehabilitated after CABG

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There is ample evidence indicating that a 3-week endurance training beneficially modifies carbohydrate metabolism in patients with ischaemic heart disease. The aim of our study was to assess training-specific effects in patients after coronary artery bypass graft surgery (CABG) with arterial hypertension (AH) in whom a problem of insulin resistance can be expected more frequently. The study was conducted in a group of 30 male patients (15 hypertensive and 15 normotensive), aged 55.5 ± 2.1 years (mean ± SEM), with BMI 26.2 ± 0.8, within 1 to 6 months after CABG. Before and after training program, the cardiopulmonary exercise test was carried out and glucose, insulin, and C-peptide blood levels, as well as binding and degradation of 125I-insulin by erythrocyte receptors, were determined. All patients were submitted to 15 training sessions on a bicycle ergometer for 3 weeks.

At the beginning of rehabilitation, hypertensive subgroup had statistically significant lower degradation of labelled insulin compared to normotensive one (6.703 ± 0.470 in hypertensive, 9.367 ± 0.430 pg 125I/1011RBCs in normotensive subgroup). It seems possible to consider this as one of indicators of the insulin resistance accompanying AH.

After rehabilitation, a statistically significant improvement in insulin resistance indicators (binding and degradation of labelled insulin) occurred only in the subgroup with arterial hypertension. There was a significant increase in insulin binding, from 0.496 ± 0.064 to 0.705 ± 0.064 pg 125I/1011RBCs (p<0.01), and degradation from 6.703 ± 0.470 to 9.644 ± 0.870 pg125I/1011RBCs (p<0.01). In this subgroup, there was also a significant increase in HDL-cholesterol level, from 43.7 ± 1.65 to 49.28 ± 2.87 mg/dL (p<0.05).

In the subgroup with AH, metabolic improvement was accompanied by a favourable modification of exercise systolic and diastolic BP measured in initial and final exercise tests at the same workload and the same drug treatment. Mean systolic BP fell from 185.4 ± 7.3 mm Hg in the preliminary test to 168.5 ± 5.0 mm Hg (p<0.05) in the final test and mean diastolic BP decreased from 106.5 ± 3.0 mm Hg in the preliminary exercise test to 100.0 ± 1.5 mm Hg (p<0.01) in the final test.

Conclusions: Rehabilitation after CABG based on the endurance training was especially efficient in hypertensive patients in whom, besides beneficial influence on the exercise blood pressure, a significant improvement in some metabolic risk factors of ischaemic heart disease was observed.

P2286 Combined endurance–resistance training increases linear isokinetic parameters of skeletal muscles in patients with chronic heart failure

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Purpose: Skeletal muscles(SM)of patients with chronic heart failure CHF) are characterized by lower maximal strength and earlier fatigue than healthy controls. These impairments are due to SM atrophy, impaired nutritive blood flow and abnormalities in histology and metabolism. Several controlled studies show improvement of these impairments by exercise training. Linear Isokinetic (LI) assessment provides important information on functional capacities of the SM such as power, force, speed and explosive force.
Methods: LI parameters of SM were measured in patients (N=25) with stable CHF (mean EF = 28,8%) before and after a 6- month exercise-training program. The physical reconditioning consisted of a combined aerobic training and a specific designed resistance training for multiple small muscle groups.
Results: Training induced a highly significant increase of Maximal Mechanical Work Capacity on treadmill of more than 38% (p=0.001) and a significant increase in Maximal Oxygen Uptake of 17% (p=0.01). LI parameters of the SM during a multifunctional test increased significantly (see table)

	Start	After	Unit	P-value	Gain
Mean Max P	323	487	Watt	0.03	+ 51%
Max Power	570	432	Watt	0.01	+ 63%
Work	347	561	Joule	0.03	+ 61%
Max Force	571	926	Newton	0.01	+ 62%
Time to Fm	0.33	0.34	seconds	ns	ns
Max explo	16940	30314	Newton/sec	0.01	+79%
Mn Expl F	1879	3423	Newton/sec	0.006	+82%
F at 0.25s	512	861	Newton	0.01	+68%
P at 0.25s	86	154	Watt	0.01	+79%

Conclusions: Combined aerobic-resistance training of patients with CHF induces beneficial effects on both maximal and sub-maximal physical performance. Patients trained in this programme move faster with more force and more power, thus performing with better locomotive coordination and with much more efficiency.NYHA functional class,sub-maximal and maximal workrate improved in these immobile patients. LI measurement of muscular performance is a valuable tool to assess functional capacity in patients with CHF.

P2287 Heart rate variability improvement in patients after surgical myocardial revascularization undergoing physical rehabilitation

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Patients after coronary artery bypass grafting (CABG) have impaired heart rate variability (HRV). The influence of physical rehabilitation on HRV in this group of patients is unknown.
The aim of the study was to assess HRV and left ventricular function in patients after CABG undergoing a 21-day program of interval training with constant workload.
Material and methods: We studied 103 patients after CABG divided into group A (72 pts) undergoing group physical rehabilitation (started 7-8 days after CABG in the centre of cardiac rehabilitation) and group B (31 pts) without rehabilitation. In all patients echocardiography, 24hr ECG recording (to assess time- and frequency-domain HRV), exercise stress test (EXT) were performed at baseline, at 21 days, and after 6 months.
Results (at baseline and at 21 days presented in the Table): At baseline time domain parameters were similar in both groups, frequency domain HRV was significantly higher in group A.

	SDNN [ms]	pNN50 [%]	EF [%]	EXT [min]	LF [ms2]	HF [ms2]
Group A (n=72)						
at baseline	55.6±19.9	0.8±1.9	49.6±10.2	6.3±3.1	146.2±96.5	31.5±28.4
p	<0.001	<0.05	<0.05	<0.001	NS	NS
at 21 days	64.9±25.8	1.1±2.8	51.7±9.6	8.0±2.7	201.6±139.0	49.7±43.7
Group B (n=31)						
at baseline	50.5±21.7	0.3±1.1	51.9±10.0	5.4±2.6	103.5±77.0	8.4±10.8
p	NS	NS	NS	NS	NS	NS
at 21 days	51.3±18.4	0.4±1.4	51.3±8.1	5.9±2.5	146.6±152.0	31.4±28.5

At 21 days time domain HRV parameters improved only in group A, whereas frequency domain HRV remained unchanged. At 6 months time and frequency domain parameters increased significantly in both groups, but they were significantly higher in patients undergoing rehabilitation.
Exercise tolerance was significantly higher in group A after rehabilitation and at 6 months. There were no differences in EF at 6 months.

Conclusions: After CABG time domain HRV is improved in the short (21 days) and long run, whereas frequency domain parameters increase at a later time. Physical rehabilitation speeds up the time domain HRV improvement and influences positively the time and frequency domain parameters in the long term follow-up (6 mths).

P2288 Should there be gender-separated cardiac rehabilitation programs?

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Background: Underrepresentation of women in cardiac rehabilitation may have different reasons. Selection mechanisms may lead to different outcomes. We investigated the benefit and course of rehabilitation of women compared to men in our outpatient cardiac rehabilitation program (OCR).
Methods: In a period of 30 months a total of 83 women (15%) and 456 men (85%) participated in an OCR. They were compared regarding risk factors, previous revascularisation, LVEF, exercise capacity, quality of life scores and complications at the beginning and at the end of OCR.
Results: Women were slightly older (62±9 years vs 60±11 years, p=0.09) and had a higher prevalence of myocardial infarction (70% vs 59%, p=0.09). Revascularisation before OCR was less often performed in women (65% vs 84%, p<0.05) due to a lower rate of CABG(17% vs 36%, p<0.001) while the proportion of PCI (48% each) was equal. In the female cohort were less diabetics (6% vs 15%, p<0.05) and ex-smokers (31% vs 44%, p<0.05), but more persisting smokers (22% vs 15%, p<0.05). There was no difference in the history of hypertension and hypercholesterolemia. LVEF was not significantly different (56,8±12,8% vs 55,3±13,8%, p=0.17), but women had a lower exercise capacity in % of predicted target workload at baseline (73.9±18 vs 78.0±18, p<0.05) and a lesser increase in % of target workload after OCR (14.3±16 vs 20.8±16, p<0.001). Quality of life scores (PLC-questionnaire, Siegrist 1996) were similar at the beginning of OCR but men had a slightly greater improvement (p=ns) in all subscores during OCR. Women experienced more noncardiac complications (7% vs 2%, p<0.05) resulting in more discontinuation of OCR (12% vs 4%, p<0.01). There was no significant difference in cardiac complications (6% vs 3%, p=0.19).
Conclusion: Women are a minority in OCR. They are older, have a somewhat lower risk profile and less previous revascularizations but similar cardiac function. They start at a lower exercise capacity which they also increase less than men during OCR. Their benefit in quality of life is somewhat less than that of male and they are more prone for noncardiac complications. Due to these differences women may often be misplaced and should probably be offered gender-specific programs.

P2289 Prevalence of venous thromboembolism among patients entering a cardiac rehabilitation program after coronary artery bypass surgery

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No specific guidelines on venous thromboprophylaxis after cardiac bypass (CABG) have been issued as in other surgical subspecialties. Few information is available about the prevalence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in postoperative rehabilitative facilities.

Aim of this study was to evaluate 1) prophylaxis habits in the surgical setting and 2) the rate of DVT and symptomatic PE in patients with a recent CABG entering a cardiac rehabilitation program.

Two hundreds and seventy consecutive patients discharged from 19 surgery units (men 81%, mean age 64±9 years, mean interval after operation 8 days) were evaluated for postoperative venous thromboprophylaxis, underwent serial bilateral legs venous ultrasound examinations (day 1 an 7 after admission, then if specific symptoms occurred; duplex and color doppler imaging adopted) and were closely observed for clinical presentation of PE in three cardiovascular rehabilitative centres. Patients with previous DVT or PE, concomitant other cardiac surgery or planned anticoagulation were excluded.

At admission, aspirin treatment (to maintain graft patency) was present in 96% of cases. In 171 (63%) cases treatment with low, fixed doses of subcutaneous heparin was reported. Of these, heparin was limited to the early postoperative period (<4 days) in 102 (38%) cases. Graded compression stockings (GCS) were prescribed in 200 (74%) cases.

DVT was detected in 47 (17.4%) patients (proximal DVT 2.6%, isolated distal DVT 14.8%), complicated in 2 (0.7%) by symptomatic PE (fatal PE 0.4%). Clots were found in contralateral leg to the saphenous vein harvest site in half of all DVT cases. Serial testing permitted to diagnose 4 (8.5%) isolated distal DVT cases lost at day 1 examination. On multivariate analysis the following variables were independently associated with the presence of DVT: female sex ($p<0.001$), length of stay in surgery units >8 days ($p<0.05$) and no adoption of heparin prophylaxis ($p<0.05$).

This study showed a high rate of DVT in patients entering cardiac rehabilitation after CABG, while symptomatic PE appeared to be an uncommon complication. Wearing monolateral GCS after CABG had limited efficacy, as clots were often localized bilaterally. The role of routine heparin prophylaxis should be extensively investigated.

P2290 Disability, emotional and cognitive factors in over-70 patients undergoing in-hospital rehabilitation after cardiac surgery

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Depression and cognitive disorders are frequently observed after cardiac surgery (CS) and may poorly affect prognosis. Elderly pts usually have more advanced cardiac disease with comorbidity and cognitive decline, carrying an increased risk for disability conditioning rehabilitation (Rehab) process. We investigated the role of disability, comorbidity, well-being self-perception, emotional and cognitive status in elderly pts early after CS on: 1) short-term functional recovery, 2) medium-term pts satisfaction about CS&Rehab process.

Methods 26 consecutive over-70 pts (75±4.5 yrs) admitted to our Rehab unit 14 (range 6-47) days after CS (9 CABG, 8 valve surgery, 9 combined) were evaluated as follows. 1. At entry: comorbidity (Charlson Index); length of stay (LOS) and complications during CS stay; disability (nursing needs: Maslow and nursing chart), ability to perform basic (BADL) and instrumental (IADL) daily living activities, cognitive function (Mini Mental State, Wais-Digit Symbol, Verbal fluency), self-perceived health-status (Euroqual questionnaire, Eq1), distance walked at 6-min test (WT1), depression (GDS-15 item). 2. In Rehab: LOS and complications, left ventricular EF, number of training sessions. 3. At discharge: 6-min test (WT2), self-perceived health-status (Eq2) and depression. 4. One month after discharge: pts satisfaction about CS&Rehab process (visual analogue 1/10).

Results The mean walked distance was 142±76m at WT1 and 266 ±123 at WT2 ($p<.0001$). WT1 significantly ($p<.05$) correlated with nursing needs (r -0.42), depression (r -0.45) and Eq1 (r 0.48), while WT2 correlated with nursing needs (r -0.57), depression (r -0.45) and disability (BADL/IADL r 0.42, WT1 r 0.69). At multivariate analysis only disability at admission resulted as independent predictor of functional recovery (r^2 0.43; $p=.001$; BADL/IADL β 0.45). No correlation was found between functional impairment-recovery and cognitive and clinical variables. Pts satisfaction was high (7.7±2.2), not related with clinical, functional, emotional and cognitive factors.

Conclusions In over-70 CS pts: 1) functional impairment at admission in Rehab unit is an indicator of care needs, emotional status and well-being self-perception; it is also a predictor of functional recovery; 2) depression influences functional capacity; 3) clinical and cognitive factors do not correlate with functional impairment and self-perception; moreover they do not affect the recovery process; 4) pts satisfaction about CS&Rehab process is not related with any of the considered clinical, functional, emotional and cognitive factors.

P2291 Functional and perceived recovery during intensive in-hospital rehabilitation after cardiac surgery in elderly

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In elderly the recovery process after cardiac surgery (CS) and Rehabilitation (Rehab) is influenced not only by cardiac conditions but also by comorbidity, cognitive decline and disability.

We evaluated the relationship between objective and subjective factors and their influence on functional recovery in 204 consecutive over-70 pts (75±3.8 yrs) admitted to intensive Rehab unit 12±7 days after CS (108 CABG, 64 valvular, 32 combined). We considered: comorbidity (Charlson index), length of stay (LOS) and complications in CS and Rehab, disability (nursing needs: Maslow/nursing chart), functional status (6-min walking test: WT1 at entry, WT2 at discharge), left ventricular EF, number of training sessions in Rehab, self-perceived health status (Euroqual questionnaire: Eq1 at entry, Eq2 at discharge) and emotional impairment (anxiety/depression, CBA-H/interview).

Results Functional capacity: the mean walked distance was 198±103m at WT1 and 287±121 at WT2 ($p<.0001$). The variables poorly but significantly ($p<.05$) associated with WT1 were: age, LOS in CS and Rehab, depression, complications in CS, nursing needs and Eq1. At multivariate analysis only nursing needs were weak, independent predictors of WT1 (r^2.14, $p<.001$, β -.21). WT2 was significantly associated with WT1, age, LOS in CS, complications in CS and Rehab, nursing needs, Eq1, Eq2 and training sessions. Multivariate analysis showed that WT1 (β 0.49), complications in Rehab (β -0.15), Eq2 (β 0.15) and training sessions (β 0.20) were independently correlated with WT2 (r^2.50, $p<.0001$). Pts perception: anxiety correlated with depression, LOS and complications in Rehab. At multivariate analysis only depression remained as independent factor (r^2.53, $p<.0001$, β 0.69). Emotions did not correlate with functional measures. Age, nursing needs and WT1 were significantly associated with Eq1. At multivariate analysis, only nursing needs were weak, independent predictors of Eq1 (r^2.15, $p<.0001$, β -.29). Eq2 correlated with age, complications in CS and Rehab, WT1, WT2 and Eq1. Eq1 resulted the only predictor of Eq2 (r^2.33, $p<.0001$, β -.42).

Conclusions During a post cardiac surgery rehabilitative program in over-70 pts: a) there is no correlation between clinical and psychological variables; b) functional impairment is strongly influenced by nursing needs which also affect the self perceived health status; c) anxiety and depression are associated but do not influence the recovery process neither correlate with well-being self-perception; d) functional recovery is influenced by disability at admission but favoured by physical training.

CARDIOVASCULAR DISEASE IN THE ELDERLY

P2292 Acute ischaemic syndromes in the elderly: The very elderly (>80yr) have different characteristics and poorer outcomes than the elderly (>70yr)

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Background and aims: Patients with acute ischemic syndromes (AIS) presenting in their 80s may have a different clinical profile to pts in their 70s. We maintained a registry of consecutive patients aged => 70 yrs hospitalized for AIS and compared baseline characteristics and clinical outcomes in octogenarians (Octo) vs septuagenarians (Septu).
Patients and methods: The registry included 255 consecutive septu (age 74.3±2.7yr) and 201 consecutive Octo (age 84.1±3.9yr) with definite or suspected AIS hospitalized in 3 internal medicine or cardiology departments in a single medical center.
Results: Octo were less likely to have classic risk factors for coronary artery disease: hypertension 129 (65.2%) vs 185 (73.7%), p=0.05, diabetes mellitus 51 (25.9%) vs 83 (33.2%), p=0.09 and cholesterol/HDL ratio was lower 4.45±1.1 vs 4.72±1.2, p=0.04. Octo also had less prior revascularization 45 (22.6%) vs 90 (35.6%), p=0.003. However Octo were sicker on presentation than Septu (Table). Coronary angiography was performed less in Octo (57, 28.6% vs 110, 44.0%; p<0.001) but prevalence of 3 vessel disease was greater (34, 58.6% vs 39, 43.3%, p=0.07). Revascularization rates were similar overall (44, 22.1% vs 64, 25.5%, ns) but surgery was performed less in Octo (11, 5.5% vs 26, 10.4%, p=0.06). Outcome over a period of 15.8±3.5 months was better in Septu than Octo (table).

Patient Characteristics and Outcomes

	CHF	Renal. Failure*	CVA/TIA**	AMI$	Death	Death/ Rehosp#
Septu (N=255)	48 (19.2%)	30 (12.3%)	19 (7.6%)	23 (9.6%)	31 (12.3%)	126 (49.8%)
Octo (N=201)	66 (33.2%)	41 (21.5%)	24 (12.1%)	40 (22.1%)	51 (25.6%)	126 (63.3%)
p	<0.001	<0.01	0.1	<0.001	0.0002	0.004

*Creatinine >1.4mg%; **Prior CVA/TIA; $CK>2X upper limit of normal; #Death or rehospitalization

Conclusions: 1. Major differences exist in baseline characteristics and clinical outcomes in consecutive septuagenarians and octogenarians hospitalized for acute coronary syndromes. 2. Coronary angiography was performed less frequently in octogenarians. 3. Late mortality was high in both groups and double in octogenarians (26% vs 12%). 4. These data are important in determining applicability of results of controlled clinical trials to these specific age groups.

P2293 Plasma levels of inflammatory C-reactive protein and interleukin-6 predict outcome in elderly patients with stroke

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C-Reactive protein (CRP) is associate with unfavorable outcome in patients with acute ischemic syndromes and in patients with chronic stable angina. Elevated CRP levels suggestive of heightened inflammatory state in vascular conditions are often associated with elevated Interleukin-6 (IL-6) levels. The predictive importance of CRP and IL-6 levels in patients with ischemic stroke has never been elucidated. To this end we studied among 647 consecutive elderly patients (>65 years) those with documented ischaemic stroke, presence of significant carotid atherosclerosis and absence of atrial fibrillation. The study population included 150 patients (74 men, 76 women mean age 74±2) Patients underwent evaluation of high sensitive CRP and IL-6 levels at baseline, during hospitalization and at discharge. In-hospital was 6%, 1 year mortality was 15% and another cerebrovascular event occurred in 12% of patients. Patients with in-hospital events had significantly higher CRP and IL-6 levels than patients without events (3.8±1.1 vs 1.9±0.9 mg/l, p<0.01 and 13.8±3.4 vs 6.3±2.1 pg/ml, p<0.01, respectively). Also CRP and IL-6 levels were significantly higher in those patients with an event within 3 months of discharge compared to those patients without an event (3.6±1.3 vs 1.1±0.7 mg/l, p<0.01 and 14.2±3.7 vs 5.4± 1.6 pg/ml, p<0.01, respectively). Both baseline CRP levels and IL-6 were predictor of future in-hospital and 3 months future cerebrovascular events while high CRP and IL-6 levels at baseline were not associated with a poor 1 year prognosis. Elevated CRP levels were associated with an unfavorable outcome only when IL-6 levels were also elevated. In a stepwise multivariate analysis IL-6 levels were stronger predictor of outcome than CRP.
In conclusion elevated CRP and IL-6 levels may identify elderly patients at increased medium term risk while do not predict one year events in this subset of patients. CRP levels predict events only when they are coupled with IL-6 levels.

P2294 Percutaneous coronary intervention in octogenarian population: comparison with elderly patients in Japan

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Background: Previous studies have suggested the octogenarian have worse outcomes of percutaneous interventions (PCI). However current outcomes of PCI for these patients are still unclear.
Method: We analyzed and compared baseline clinical, angiographical results of 288 consecutive octogenarians (mean age 84.3±4.8 years and 54.9% male) with those of 902 consecutive elderly patients aged from 70 to 79years (mean age 74.7±4.7 and 61.5% male) undergoing PCI from April 1999 to April 2001. The octogenarian group had a higher incidence of LVEF<40%, hypertension, DM, history of CHF, recent MI (<14 days) and total occlusion. Stent and Rotablator use was similar in both groups.
Results: See the table.

octogenarian

	Elderly (70-79 yrs) n=1402	Octogenarians (80> yrs) n=388
Angiographic success (%)	98.8	98.5
Clinical success (%)	98.4	97.4
MACE at 30 days (%)	0	0
MACE at 180 days (%)	12.5 (all: re-PTCA)	10.6 (all: re-PTCA)
Vascular access complications (%)	3.8	4.4
Storoke (%)	0.3	0.3
Event free survival (6 months) (%)	83.4	84.7

MACE: Major Adverse Cardiac Events (death/MI/CABG/re-PTCA)

Conclusion: In octogenarians, PCI can be performed with high success rate without increasing MACE and vascular complications compared with elderly (from 70 to 79 years) patients.

P2295 The presentation and aetiology of heart failure in the elderly – The Hastings heart failure study

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Introduction: The presentation and aetiology of heart failure in a district general hospital particularly in the elderly is unknown.
Methods: Data was collected prospectively, over a one year period, on all patients in an ageing community of 185,000 presenting to Conquest hospital, Hastings either as an in- or out-patients. Each patient was panelled by one of 2 consultant cardiologists to confirm the validity of diagnosis using ESC guidelines. The history, examination, investigation findings and the contributory causes (aetiology) to heart failure in each patient were recorded.
Results: 1251 hospital presentations of patients suspected to have heart failure were identified. After validation and correction for multiple admissions per patient, 434 patients were confirmed to have true left ventricular systolic dysfunction. The age range was 38 to 101 (average 79, median 80) with prevalence increasing sharply by age. 71% (308) of all patients were older than 75 years old. 49% (214) of all patients were male and 51% (220) female, with an average age of 76 for men and women 82. Dyspnoea was present in 90% of all presentations. NYHA scores were: I – 9%; II – 12%; III – 25% and IV 54%. The resting ECG was abnormal in 95% of all patients and the CXR was abnormal in 95%.
The contributory causes to HF (numbers and percentages) in the elderly is shown below:

Diagnosis:	IHD	HT	Valve	DCM	AF	Alcohol	Unknown
>75:	145 (47%)	116 (38%)	81 (26%)	3 (1%)	146 (47%)	1 (0.5%)	21 (7%)

Conclusion: The Hastings HF study reinforces the dramatic increase in prevalence of systolic HF with age. More than half of all patients identified were in NYHA Class IV. The commonest aetiology in HF is IHD but in >75 multifactorial aetiology is more common. Management strategies for HF need to acknowledge the prevalence, age and complexity of heart failure in the elderly patient in a DGH.

P2296 Patients with 76 or more years admitted with congestive heart failure have a clinical profile different than their younger counterparts

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Introduction: Heart failure (HF) is a rapidly expanding syndrome. We need information to design adequate preventive strategies and differences related with age are specially relevant in this condition.
Methods: A total of 1,953 HF or related diagnosis were done among pts admitted consecutively to our institution during 1 year period. Hospital records were collected and retrospectively checked. We excluded 454 pts in whom the presence of HF could not be objectively determined, 69 pts with acute myocardial infarction and 72 pts in whom some data were not available. Therefore we studied 1,358 admissions in 1075 pts (1.27 admission per pt).
Results: Mean age was 74.7 ± 11.6 years. Patients aged >75 y were more frequently females (68 vs 48%). We observed a higher prevalence of: stroke (14 vs 10%), aortic stenosis (11.6 vs 6.5%), cardiomegaly (88 vs 81%) and LVEF >0,4 (65 vs 51%), leg edema (68 vs 62%) and rales (80 vs 73%). They also received diuretics more often (88 vs 80%). However, these older pts had a shorter hospital stay (13.8 vs 17.4 days) and less admissions in the cardiology department (21 vs 31%). We observed a lower prevalence of risk factors (smoking -8.5 vs 25%-, hyperlipidemia -7.4 vs 15%-, severe obesity -4.0 vs 8.7%-, and alcoholism -3,4 vs 13%-), coronary artery disease: (severe coronary stenosis -4 vs 12%- and previous CABG -1.3 vs 8.9%-), and liver disease (2.2 vs 7.5%). Echocardiography was performed less frequently (55 vs 78%) and they received less betablockers (2 vs 7%) and anticoagulants (11 vs 43%). at discharge All differences were significant (stroke and leg edema p=0.05, all the others p<0.01). We found a similar use of ACE inhibitors (67 vs 72%, p=0.25)
Conclusions: 1) Patients with 76 or more years admitted with HF have a different clinical profile, with more comorbidity, less ischemic heart disease and better ejection fraction than their younger counterparts. 2) They undergo echocardiography less frequently. 3) At discharge they receive more diuretics and less betablockers and oral anticoagulants, while the use of ACE inhibitors is similar in both groups.

P2297 Acute ischaemic syndromes in the elderly: Is survival better in patients selected for angiography?

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Background: The role of interventions in the elderly with acute ischemic syndromes (AIS) is not clear and may be misrepresented in clinical trials due to high selection bias. We examined characteristics and outcomes in consecutive pts included in a registry of AIS in the elderly.
Patients and Methods: The registry included 251 consecutive septuagenarians and 201 consecutive octogenarians with definite or suspected AIS hospitalized in 3 internal medicine or 1 cardiology department in a single medical center over 1 calendar year. Mean age was 78.6±5.9 yr. Outcomes were examined at a mean time of 15.8±3.5 months.
Results: Coronary angiography (angio) was performed in 168 pts (37.2%) of whom 106 (63.1%) underwent revascularization (68.2% PCI, 31.8% CABG). Patient characteristics and outcomes are presented in table.
In pts undergoing angio without subsequent revascularization (N=62) mortality was less (7.8%) than in the no angio cohort 61 (21.7%) (p=0.01).

Patient Characteristics and Outcomes

	Age(SD)	CHF	AMI*	CVA#	Death	Rhsp**	D/Rhsp$
Angio+ (%)	76.9 (4.9)	25 (15.1)	33 (23.1)	11 (6.6)	21 (12.6)	79 (47.3)	89 (53.3)
Angio- (%)	79.6 (6.3)	88 (31.3)	53 (19.3)	32 (11.4)	61 (21.6)	138 (48.9)	161 (57.1)
p val	0.0001	0.0001	0.36	0.095	0.016	0.74	0.43

*CK>2X upper limit of normal; #Prior TIA or CVA; **Rehospitalization; $Death or rehospitalization

Conclusions: In a registry of consecutive elderly patients (mean age 78.6yr) with acute ischemic syndromes, patients selected for coronary angiography were 1. Younger, had less CHF and less prior cerebrovascular disease 2. Pts undergoing angio had a better 15 month survival, irrespective of whether revascularization was performed 3. Repeat hospitalization was similarly high in patients with and without angiography and whether revascularization was performed or not.

P2298 Effect of multifactorial cardiovascular prevention in 75+ patients: one-year medication and risk factors results of the DEBATE study

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Background: There has been a paucity of elderly individuals in cardiovascular prevention trials. Therefore, the aim of the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study is to test the applicability and effectiveness of established cardiovascular disease (CVD) prevention methods in patients aged 75 and over. We report here the risk factor and medication changes in the intervention and control groups after the first year.
Methods: This population-based study has randomized 400 home-dwelling CVD patients, aged 75, 80, 85, and 90 years at baseline (mean age 80 years, 65% women), for a multifactorial intervention trial (Am Heart J 2001;142:945-51). Of the participants at baseline, 82% had coronary heart disease, 37% history of stroke, 19% NIDDM, and 45% hypertension; only 6% were current smokers. Before randomization, 67% used aspirin, 40% beta-blockers, 14% ACE inhibitors, and 20% lipid-lowering drugs. In the intervention group (n=199), lifestyle factors and CVD treatments are individually tailored by geriatrician-internist according to current guidelines; the control group (n=201) receives the usual care. The primary endpoint will be a composite of major CVD, secondary endpoints include permanent institutionalization, decline in cognitive and physical function, and quality of life.
Results: One-year status of treatments and risk factors is available from 90% of the both groups. In the intervention group as compared to the control group, there has been a significant increase in the use of statins (currently 56% vs. 19%, p<0.0001), aspirin (71% vs. 61%, p=0.03), beta-blockers (60% vs. 47%, p=0.008), and ACE inhibitors (23% vs. 14%, p=0.01). In the intervention group serum total cholesterol and LDL-cholesterol were reduced significantly (p<0.0001 vs. control group), and pulse rate was slightly decreased (p=0.04). Serum high-sensitive C-reactive protein increased significantly less (p=0.009) in the intervention group during the first year. In contrast, body mass index, blood pressure, and blood glucose were not statistically different between the groups. Also serum creatinine, potassium, sodium, and liver enzyme values were similar in the two groups
Conclusion: These interim results suggest that it is feasible and safe to further improve current evidence-based treatments in the oldest cardiovascular patients in real life. Of the risk factors, serum cholesterol and C-reactive protein showed favourable changes in the intervention group. The results are promising for a reduction of clinical endpoints during further follow-up.

P2299 A1 and A2a adenosine receptor gene expression during cardiovascular aging

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Cardiovascular aging is associated with progressive structural and functional modifications that may contribute to an increased prevalence of heart failure (HF), a situation characterized by excessive catecholamine stimulation. Since HF is also characterized by a reduction of the cardioprotective effects of adenosine (Ado), which are at least in part mediated by the antiadrenergic actions of Ado A1 receptor (A1R) activation and modulated by Ado A2a receptor (A2aR) stimulation, we investigated the relationships between Ado A1R and A2aR gene expression and cardiac function during cardiovascular maturation and aging. Left ventricular (LV) end-diastolic (EDD) and end-systolic (ESD) internal dimensions, and LV fractional shortening (FS, %) were evaluated by M-Mode echocardiography in 2, 5, 12, and 21 month-old Sprague-Dawley rats (2M-old, 5M-old, 12M-old and 21M-old, respectively; n=10 per group). After LV catheterization for the evaluation of systolic LV pressure (LVP), A1R and A2aR mRNA levels were measured in LV myocardial fragments by RT-PCR (densitometric units normalized for the reference gene GAPDH).
Results are shown in the table (means+SEM; *p<0.05 vs 2M-old).

Table

	EDD (mm)	ESD (mm)	FS (%)	LVP (mmHg)	A1R	A2aR
2M-old	7.5+0.2	4.2+0.1	42+1	98+2	1.42+0.14	0.60+0.03
5M-old	8.1+0.2	4.4+0.1	38+2	101+3	1.11+0.05	0.37+0.03*
12M-old	8.5+0.2	4.7+0.2*	39+2	102+3	2.02+0.12*	0.41+0.02*
21M-old	8.8+0.2*	5.1+0.2*	35+2*	105+4	2.11+0.20*	0.40+0.02*

Aging was associated with progressive reduction in systolic function and increases in both end-diastolic and end-systolic LV dimensions, at comparable systolic LV pressure. Concomitantly, Ado A1R gene expression was increased, while Ado A2aR mRNA levels were reduced. These opposing changes in Ado A1 and A2a receptor gene expression during aging indicate that a modification of their cross-talk may be associated with LV morpho-functional alterations and progressive loss of adenosine cardioprotective mechanisms.

P2300 Differences in coronary risk factors between middle-aged and elderly individuals. The CARDIO2000 study

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Background: It is suggested from several investigators that the relative risks of cardiovascular events in elderly are much different compared to the others. In this work we aim to evaluate differences in the coronary risk factors between elderly and middle aged people, in a Mediterranean population with high life expectancy.

Methods: During 2000-01, we randomly selected 848 hospitalised patients (695 males, 58±10 -153 females, 65±9 years old) for first event of acute coronary syndromes (ACS) and 1078 paired, by sex-age, hospitalised controls without CHD (CARDIO2000), from all the Greek regions. In order to evaluate differences in the risk factors between elderly and the rest of the subjects, we developed multivariate risk models, using "dummy" variables as indicators of age group.

Results: 370 (43%) of the patients and 408 (38%) of the controls were over 65 years old (mean age (SD): 70 ± 4 and 69± 3, respectively). The sex ratio (males/females) was 7-to-3 in the elderly, while it was 4-to-1 in the < 65 years old patients. The following table presents differences in the effect of the investigated risk factors between middle –aged and elderly people.

	Age < 65 yrs		Age > 65 yrs		Differences
Risk factor	OR	P-Value	OR	P-Value	P-Value
Smoking (Y/N)	2.41	0.0001	1.56	0.017	< 0.05
Hypertension (Y/N)	2.04	0.012	1.99	0.001	NS
Diabetes mellitus (Y/N)	1.84	0.017	3.22	0.001	< 0.01
Sex (male-female)	1.41	0.018	2.11	0.001	< 0.05
Age (10-years)	1.04	0.023	1.19	0.001	NS
Physical inactivity (Y/N)	1.12	0.023	1.14	0.51	NS
Unhealthy diet (Y/N)	1.21	0.024	1.76	0.005	< 0.05
Hypercholesterolemia (Y/N)	3.95	0.031	2.75	0.001	< 0.01
Social status (low/high)	1.44	0.032	1.22	0.166	< 0.05
Depression (Y/N)	1.22	0.035	1.51	0.027	< 0.05
BMI (Kgr/m^2)	1.02	0.039	1.00	0.78	NS

Conclusions: In elderly subjects some common risk factors like smoking, sex, diabetes mellitus, unhealthy diet, depression and BMI seem to have different impact on coronary risk than in younger subjects. Recognition of the differences that occur in periods throughout the life span may contribute to understanding their causes and devising more effective strategies for the primary prevention

PROGNOSIS IN HEART FAILURE

P2301 Prognostic value of left atrial functional parameters in congestive heart failure

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Background: Prognostic significance of the left ventricular performance in patients (pts) with congestive heart failure (CHF) is well established. However, it has not been clarified whether left atrial (LA) dysfunction influence the mortality in these pts.

The aim of our study was to assess the contribution of the parameters of LA function to the prediction of survival in pts with severe CHF.

Methods: We prospectively studied 172 pts (mean age 60.2±0.8, male 120) in sinus rhythm with dilated cardyomyopathy of ischemic (n=132) or nonischemic (n=40) origin and NYHA III-IV functional class CHF. LA end-systolic dimension, volume, late diastolic (A) transmitral flow velocity, LA kinetic energy (LAKE), mitral regurgitation (MR) and also atrioventricular place displacement (AVPD) were obtained using M-mode, two-dimensional and Doppler echocardiography. LAKE was calculated using the formula=1/2 LA stroke volume x1.06 x A^2, where the A-transmitral Doppler A velocity. MR was quantified as a MR area/LA area ratio.

Results: During a mean follow-up period of 50±14 months 58 (33.7%) pts died from cardiac causes. Pts with cardiac events had a more impaired LAKE (4.7±0.8 kdyn/cm/sec vs. 9.1±1.1 kdyn/cm/sec, p<0.001), transmitral filling pattern, depicted by A velocity (29.3±3.6cm/sec vs. 39.2±3.1 cm/sec, p<0.05), and AVPD (5.5±0.8mm vs. 8.9±1.1mm, p<0.01). The MR was markedly severe in nonsurvivors than in survivors (0.41±0.05 vs. 0.2±0.04, p<0.02). In pts free of cardiac events lower LA dimension (62.6±5.3mm vs. 76±4.2mm) and volume (93.6±7.1ml vs. 116±8.3ml, p<0.05) were found. In the univariative Cox proportion hazard model all of these parameters were found to be significant prognostic indicators of survival. However, the multivariative Cox analysis revealed that only LA enlargement, LAKE and AVPD were the significant independent predictors of cardiac death. Kaplan-Meier survival curves demonstrated a survival rate of 68% for pts with LA dimension>70mm and volume>110ml and 87% for those with dimension<70mm and volume<110ml (p<0.01). Similar probability of survival (p<0.01) was shown in pts with LAKE>6.5 kdyn/cm/sec (85%) and AVPD>7.0mm (82%) and in those with LAKE<6.5 kdyn/cm/sec (62%) and AVPD<7.0mm (64%).

In conclusion, LA parameters are the powerful predictors of survival in pts with CHF. LA enlargement allows for identification a high-risk subgroup of pts with a worse outcome. In addition, lower LAKE and AVPD provide similar prognostic information.

P2302 Haemoglobin predicts survival in patients with chronic heart failure with a U-shaped curve: a substudy of the ELITE II trial

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Background: The correction of anaemia in chronic heart failure (CHF) is associated with an improvement in symptoms and cardiac function. The relationship between haemoglobin and survival in CHF, and whether there is an optimal range, is not known.

Methods: We analysed haemoglobin concentrations in 3044 patients recruited in the Evaluation of Losartan In The Elderly (ELITE II) trial. Patients of mean age 71.5±6.8 years (±SD) and New York Heart Association (NYHA) class 2.5±0.6 were enrolled from June 1997 to May 1998 and followed-up for survival (range 1 to 780 days, median 551).

Results: The mean haemoglobin level was 14.0±1.6 g/dL (males: 14.3±1.5, females: 13.3±1.4 g/dL; p<0.0001). Overall, there were 513 patients (16.9% of the study population) with a haemoglobin level less than 12.5 g/dL (257 males [12.2% of all males]; 256 females [27.1% of all females]). There were 82 females (8.7% of all females) with a haemoglobin level less than 11.5 g/dL. In univariate analysis, age, NYHA class, serum creatinine, left ventricular ejection fraction (all p<0.0001) and sex (p=0.046) all predicted survival. Haemoglobin as a continuous variable for all patients was not a significant prognostic marker (p=0.26). However, subdividing patients according to 1.0 g/dL increments of haemoglobin revealed a U-shaped mortality curve, with 14.5-15.4 g/dL having the best prognosis (2 year survival 85%; 95% CI 81 to 89%), independent of age, sex, NYHA class, left ventricular ejection fraction, creatinine, co-existing chronic obstructive pulmonary disease and treatment allocation (p<0.001). Patients in the lowest (<12.5 g/dL) and highest (>15.4 g/dL) haemoglobin groups had the worst survival (75% and 76%, respectively, at 2 years). Further analysis identified a haemoglobin of 14.5 g/dL as optimal for survival in CHF.

Conclusions: Anaemia is frequently observed in patients with CHF and relates to a poor prognosis. Haemoglobin is an independent predictor of mortality for patients with CHF. The relationship is not linear but follows a U-shaped curve, with anaemic and polycythaemic patients having the worst survival. It may be important to have a specific target range for haemoglobin when treating anaemia in CHF.

P2303 Anaemia is an independent predictor of poor outcome in patients with chronic heart failure

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Background: Mild anaemia frequently occurs in patients with chronic heart failure (CHF), particularly in the advanced stages of the disease. The correction of anaemia with erytropoietin may be possible. The aim of this study was to assess prospectively the relationship between the prevalence of anaemia (haemoglobin level <= 120 g/l) and prognosis in an unselected CHF population.
Methods: All consecutive patients with a diagnosis of CHF admitted to our department between January and April 2000 were considered for the present study. Those with secondary causes of anaemia were excluded. Patients were followed-up until November 2001 (>18 months in all survivors), and the endpoint of the study was all-cause mortality.
Results: One hundred and seventy six patients were enrolled (120 men, mean age: 63 yrs; New York Heart Association [NYHA] class I/II/III/IV: 14/82/52/28; left ventricular ejection fraction [LVEF]: 41%, CHF of ischaemic aetiology in 62%). In the whole population the mean haemoglobin level was 140±16 g/l. Anaemia was found in 18 (10%) patients, and was significantly more common in women than in men (18% vs 7%, respectively, p=0.02) and in those with most severe CHF symptoms (frequency in NYHA I/II/III/IV: 0%/9%/10%/21%, respectively, NYHA IV vs I-III, p=0.03), but not related to the other clinical indices. Univariate analysis revealed NYHA class III-IV (hazard ratio 3.9, 95%CI: 1.7-9.4, p=0.002), low LVEF <= 30% (hazard ratio 2.7, 95%CI: 1.2-6.2, p=0.02) and anaemia (hazard ratio 2.9, 95%CI: 1.2-7.2, p=0.02) as predictors of 18-month mortality. In multivariate analysis, anaemia remained an independent predictor of death when adjusted for NYHA class and LVEF (hazard ratio: 2.7, 95%CI: 1.1-6.8, p=0.03). In anaemic patients, 18-month survival was 67% (95%CI: 45-89%) compared to 87% (95%CI: 81-92%) in patients with a normal haemoglobin level (p=0.016).
Conclusions: Mild anaemia is a significant and independent predictor of poor outcome in unselected patients with CHF. Correction of low haemoglobin level may become an interesting therapeutic option for anaemic CHF patients.

P2304 Prognostic impact of right ventricular disfunction in patients with ischaemic and non ischaemic left ventricular disfunction

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Background: Previous observations by our group reported: 1) a higher prevalence of right ventricular (RV) dysfunction in idiopathic dilated cardiomyopathy (IDC) compared to ischemic heart disease (IHD); 2) a significant negative prognostic impact of RV dysfunction in patients (pts) with IDC. Other published studies observed that RV dysfunction is a powerful prognostic marker in heart failure. We sought to investigate the prognostic role of RV function: 1) compared to LV function; 2) in IDC compared to IHD.
Methods: We studied 193 consecutive pts (mean age 57±12 yrs; 83% males) enrolled because of a left ventricular (LV) ejection fraction (EF) <45% secondary to IHD (86 pts, 44%) or IDC (107 pts, 56%). Coronary anatomy was documented in all cases, and 70% of IDC pts underwent endomyocardial biopsy to rule out myocarditis. RV function was assessed angiographically based on Ferlinz's method (normal reference for RV EF in our laboratory: 53±6%). LV and RV parameters were entered in a multivariate analysis according to the Cox proportional hazard method. The end-point considered was transplant-free survival (TFS).
Results: LV EF was 31±9% and RV EF was 38±12%. Mean follow-up was 33 months (range 12-126 mo). Fifty-five events were recorded: 36 cardiac deaths, 3 non-cardiac deaths and 16 transplants. Thus, TFS was 72%. At univariate analysis, significant predictors of TFS were: RV end-diastolic volume (EDV) (p=0.001) but not LV EDV (p=0.108), RV end-systolic volume (ESV) (p<0.0001) and LV ESV (p=0.022), RV EF (p=0.002) and LV EF (p=0.004). At multivariate analysis, RV function was an independent predictor of TFS (EDV: p=0.001; ESV: p<0.0001; EF: p=0.003), but not LV function (ESV: p=0.800; EF: p=0.085). When etiology (IDC vs CHD) was entered in the model, the results did not show any significant change.
Conclusions: In our series, RV function appears to be more powerful than LV function as a predictor of survival, regardless of the etiology of LV dysfunction. These results are intriguing, especially for patients with IHD, which is notoriously characterized by an almost exclusive involvement of the LV.

P2305 Minor myocardial damage detected by troponin T is a powerful predictor of long-term prognosis in patients with decompensated heart failure

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Background: Progression of chronic heart failure (CHF) is characterized by frequent hospitalization for decompensation and high mortality. Clinical deterioration is triggering by many factors that could promote ongoing myocytes injury.
Aim: We sought to determine whether a specific marker of cardiac injury, cardiac troponin T (cTnT), would be associated with long-term prognosis in patients admitted for decompensated CHF.
Methods and Results: One hundred and eighty-four patients with decompensated CHF in the absence of an acute coronary syndrome were enrolled. A cTnT value >=0.1 ng/mL in samples drawn at 6, 12 or 24 hours after hospitalization was considered abnormal and it was found in 58 patients (31.5%, Group 1). There were no significant differences between Group 1 and patients with cTnT <0.1 ng/mL (Group 2) in terms of demographic and clinical data, and NYHA functional class. During a median follow-up of 9 months, the mortality in Group 1 and 2 was 31% and 17.5% (p=0.038; OR=2.13, 95% CI, 0.97-4.69). The cumulative 3-year free-CHF readmission survival in Group 1 and 2 was 53% and 25% (log rank test p=0.015). In a Cox proportional hazard model, poor tissue perfusion (RR=2.46, CI95%=1.31-4.6), previous infarction (RR=1.99, CI95%=1.02 - 3.9) and cTnT >= 0.1 ng/mL (RR=1.74, CI95%=1.05 - 2.9) emerged as the independent predictors of long-term outcome
Conclusions: One third of patients with decompensated CHF had elevated levels of cTnT. This subgroup was clinically undistinguished from those without myocardial damage. cTnT >=0.1 ng/mL was an independent long-term prognostic marker and it suggest a role of biochemical stratification in this setting.

P2306 The prognostic value of troponin T and echocardiography in acute pulmonary oedema

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Background: Elevated troponin T levels and decreased LV function have successfully predicted elevated risk in acute coronary syndromes, however their independent and combined prognostic value in patients presenting with pulmonary edema (PE) is unknown. This study examined the predictive value of troponin measurement and echocardiography in patients presenting with PE.
Methods: Records of all patients admitted to the CCU with a diagnosis of acute pulmonary edema (PE), measurement of TnT, and echocardiographic study were reviewed. Patients with ST elevation on admission ECG or severe AS were excluded. 124 patients formed the study group (mean age 73.5 ± 10.8, 61M/63F) and six month telephone follow-up of clinical status was performed.
Results: Elevated TnT levels (> 0.1 ng/ml) were noted in 53 patients (42.7%). During six months of follow-up, this group had a significantly increased incidence of ischemic cardiac events (cardiac-related death, non fatal MI or acute coronary syndrome) (26 cases (49.1%) vs 19 cases (26.8%)) compared with the TnT negative group.(p< 0.01) Moderate or severely reduced LV function (75 patients) was also a predictor of recurrent ischemic events with an incidence significantly higher in this group as compared to patients with normal or minimally reduced LV function (35 cases (46.7%) vs 10 cases (20.4%)). (p< 0.04) When cardiac function and TnT levels were analyzed together, the power of prediction was significantly improved. Only 3 (9.7%) of 31 patients with normal heart function and normal levels of troponin, had recurrent ischemic events compared with 19 patients (54.3%) among those with both reduced LV function and elevated TnT. (p< 0.002) Neither reduced LV function or elevated troponin T predicted recurrence of pulmonary edema.
Conclusions: In patients with pulmonary edema, elevated TnT and decreased LV function are independent predictors of recurrent ischemic events and combining provides additive predictive power as compared to each predictor alone. Patients with these findings require a more agressive therapeutic approach while the low event rate in patients with normal troponin and LV function, these patients may be managed more conservatively.

P2307 Risk stratification in asymptomatic or mild symptomatic left ventricular dysfunction: interleukin-6 is a strong predictor for long-term mortality

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Background: Even after introducing ACE-inhibitors and beta-blockers into heart failure treatment, the mortality rate remains high in patients (P) with congestive heart failure. Therefore risk stratification is warranted to identify high risk P for death in an early stage of heart failure. Aim of the study was to examine the prognostic significance of neurohormones and cytokines in P with asymptomatic or mild symptomatic left ventricular dysfunction (LVD).
Patients and methods: 529 P with an asymptomatic (NYHA I) or mild symptomatic (NYHA II) LVD (ejection fraction [EF] <=45%) admitted to a nonuniversitary tertiary care hospital were prospectively registered. All P were clinically stable and on optimized medical treatment for LVD when blood samples for neurohormones and cytokines were obtained (94% ACE-inhibitor, 56% beta-blocker, 66% diuretics, 59% digoxin and 4% spironolactone). Mean follow-up time was 27 months. P were stratified into two groups according to the median concentrations of the different neurohormones and cytokines. Then multiple logistic regression for all-cause mortality was performed adjusted for age, gender, concomitant diseases and medication.
Results: During the follow-up period of 27 months, 134 (25%) P died.

	Odds Ratio	95% Confidence Interval
Interleukin-6 > 8.6 ng/l	4.1	1.8 - 9.2
EF < 30%	2.3	1.2 - 4.7
Age > 70 years	2.2	1.1 - 4.6
Endothelin > 6.8 ng/l	2.1	1.1 - 4.3
TNF-alpha > 2.5 ng/l	1.9	0.9 - 4.0
Norepinephrine > 307 ng/l	1.9	0.9 - 3.7
ANP > 296 ng/l	0.7	0.4 - 1.5

Multiple logistic regression for all-cause mortality adjusted for age, gender, EF, concomitant diseases and medication

Conclusion: 1. Every fourth P with asymptomatic or mild symptomatic LVD was dead after about two years. 2. In a multivariate analysis a high level of Interleukin-6 was the strongest predictor for all-cause mortality. 3. Among neurohormones, endothelin was best associated with a worse prognosis, having a similar prognostic impact on mortality as a low EF or increased age.

P2308 Smoking status and long-term outcome in a consecutive series of patients with acute myocardial infarction

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Background: Cigarettes smoking is one of the most important risk factors for cardiovascular disease. Although it is well recognized that continued smoking confers an adverse prognosis after coronary angioplasty (PCI) in pts with acute myocardial infarction (AMI), recent studies suggest that smokers had better immediate and short-term outcome than nonsmokers, a phenomena so called "Smoker's Paradox". No data exist regarding the relationship between smoking and long term prognosis after AMI. Aim of our study was to evaluate the effects of smoking status on long-terms prognosis in pts with AMI treated with either thrombolysis (154 pts) or PCI (175 pts).
Methods: We evaluated 329 consecutive pts (288 men, 57.6±11.9 years). Two groups were defined according to smoking status before AMI: Smokers (201 pts) and No-Smokers (128 pts). In-hospitals complications were defined as: cardiac death, re-AMI, need of new myocardial revascularization, major ventricular arrhythmias, and heart failure. Major adverse cardiovascular events (MACE) were defined as cardiac death, re AMI, and a new myocardial revascularization. Long-term clinical outcome was based on MACE occurrence rate and obtained in 79% of Smokers and 83% of No-Smokers, during a 20 + 14 months follow up (FU). FU was based on a direct systematic review of all pts clinical documentation during the study period and by a telephone or direct pts interview at the end of FU.
Results: Smokers were younger (55.9±11 years vs 60±12.7 years, respectively, p = 0.001) with prevalence of male sex (94.9% vs 79.2%, p < 0.0001), a lower incidence of diabetes (12.9% vs 23.4%, p = 0.013) and hypercholesterolemia (21.9% vs 35.2%, p = 0.008) but with a higher incidence of previous angina (35.3% vs 24.2%, p=0.034). This group showed a non significant lower incidence of in-hospital events (30.3% vs 36.7%, p = NS). At long-term FU smokers had a significant lower incidence of MACE (18.9% vs 31.1%, p = 0.004). At univariate analysis, presence of diabetes (36% vs 22% p=0.039) and thrombolisys (31% vs 17%, p=0.048) were negative prognostic factors. At multivariate analysis smoking status (p = 0.005) and thrombolysis (p = 0.049) were significant predicting factors, positive and negative respectively, of long-term clinical outcome.
Conclusion: The smoking status was associated to a better long term prognosis confirming the existence of a "Smoker's Paradox". A younger age at presentation, a lower incidence of diabetes and hypercholesterolemia may account for such a paradox.

P2309 Long-term intermittent dobutamine infusion combined with oral amiodarone for end-stage heart failure. A randomized double blind study

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Background: Agents with positive inotropic effect have consistently been shown to increase mortality when administered chronically to patients with heart failure. Although controversial, the use of intravenous inotropes as a palliative measure in the small subset of patients with truly end-stage heart failure continuous to be a common practice and may be appropriate. A non randomized study has showed that long-term intermittent dobutamine infusion combined with oral amiodarone, improves the survival of patients with end stage heart failure.The purpose of this randomized double blind study was to evaluate prospectively the effects of long-term intermittent dobutamine infusion (IDI) combined with oral amiodarone in patients with congestive heart failure (CHF), refractory to standard medical treatment.
Methods: Thirty patients with decompensated CHF refractory to standard treatment who could be weaned from dobutamine therapy after an initial 72-hr infusion, were randomized in a double blind manner to Group 1, treated with intravenous placebo infusion for 8 hours every 14 days, and to Group 2, treated with intermittent dobutamine infusion 10ìg/kg/min, for 8 h every 14 days. All patients were treated with oral amiodarone, 400mg/d, started at least 2 weeks before their randomization. Worsening of the patients clinical and/or hemodynamic condition was followed by weekly infusions and if there was no improvement the label was opened and the patients were placed on dobutamine weekly infusions.
Results: There were no differences in baseline clinical, hemodynamic and biochemical characteristics between the two groups. The left ventricular ejection fraction was 24 ±5% and 23±6% in Group 1 and 2 respectively (p=0.563); mean pulmonary capillary wedge pressure 30±8 mmHg and 28±8 mmHg (p=0.528); systolic blood pressure 98±13mmHg and 99±18mmHg (p=0.839); cardiac index 2.2±0.7lt/min/m^2 and 2.1±0.6lt/min/m^2 (p=0.719). The estimated probability of survival at one year was 21% for group I versus 69% for group II, with a median survival time of 20.5 and 52 weeks respectively p=0.007.
Conclusions: Long-term IDI combined with amiodarone added to conventional drugs improves survival of patients with severe CHF.

P2310 Effect of subsequent pregnancy in patients with documented peripartum cardiomyopathy – a prospective echocardiographic and cytokine evaluation

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Objective: To assess the effect of subsequent pregnancy on maternal left ventricular function and plasma levels of TNF-α in patients with previously diagnosed peripartum cardiomyopathy (PPC).
Background: Peripartum cardiomyopathy is a disorder of unknown etiology, and has been reported to be more frequent in African women. Little is known about the time course pattern of left ventricular function in patients with PPC. Serial cytokine measurements have not been done previously in this group of patients.
Methods: We prospectively followed 59 consecutive black women with PPC. Echocardiograms, clinical assessment and cytokine measurements were done at baseline and after 6 months of therapy. After clinical treatment, patients were advised to avoid new pregnancies and a follow-up was obtained. In the patients that had a subsequent pregnancy, echocardiography was performed at onset of the pregnancy (8 weeks), end of pregnancy (8 months), one and three months post partum. At the same time blood for cytokine measurements was taken.
Results: There were 6 subsequent pregnancies in patients aged 26 to 39 years that occurred 1-2 years after clinical treatment of PPC. Four of the 6 patients had a persistent cardiomegaly and impaired ejection fraction (38.4%±6%, n=4 and 56.5%, n=2) at the onset of the subsequent pregnancy. A new pregnancy was initially well tolerated in all patients. None of the patients presented with preeclampsia or worsening heart failure during the pregnancy. The ejection fraction at 8 months of pregnancy remained unchanged (41±6%, n=4 and 54.5%, n=2). One month post partum there was a significant deterioration in the EF in all but one patient (26.5±5%, n=5 and 62.1%, n=1). Three months post partum 2 of the 6 patients died due to heart failure with no improvement in the EF in the remaining patients (25.5±5%, n=4). TNF-α plasma levels were 2.4±1.1 pg/ml at onset of subsequent pregnancy (n=6) and 2.3±0.9 pg/ml at 8 months (n=6). There was a significant increase in the TNF-α plasma levels to 6.8±2.4 pg/ml one month post partum (n=6) and 6.1 ±0.9 pg/ml three months post partum (n=4).
Conclusion: Subsequent pregnancy in this group of patients with PPC had a devastating outcome. The deterioration of left ventricular function occurred in all patients post partum and was accompanied by a significant rise in TNF-α plasma levels.

P2311 Incremental prognostic role of endogenous ouabain-like factor in idiopathic dilated cardiomyopathy towards heart failure progression

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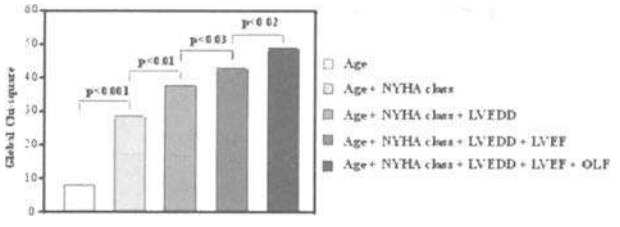
Plasma levels of endogen ouabain-like factor (OLF) have been demonstrated to be increased in patients with heart failure. No data are available so far as far as their prognostic role is concerned. We sought to verify the predicting value of OLF towards heart failure worsening in a group of patients with idiopathic dilated cardiomyopathy. We prospectively analysed 126 consecutive patients (age 51±15 years; NYHA class 1.9±0.7) with idiopathic dilated cardiomyopathy (WHO criteria), while receiving optimal treatment. Left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD), and OLF plasma levels were evaluated. The progression towards heart failure (worsening in clinical conditions leading to one of the following: sustained increase in conventional therapies, hospitalization, cardiac transplant, death) was considered as end point. After 13±5 months of follow-up, 6 patients had sustained increase of conventional therapy, 16 hospitalization for heart failure, 3 cardiac transplant and one died after heart failure worsening. At univariate analysis, age (HR:1.05; CI:1.01-1.08), NYHA class (HR:5.82; CI:2.92-11.6), LVEDD (HR: 3.35; CI:2.07-5.40), LVEF (HR: 0.89; CI:0.85-0.94) and OLF (HR: 1.005; CI:1.004-1.007) were significantly related to events. By Cox multivariate analysis, OLF was independently associated with heart failure progression (HR: 1.003; CI:1.001-1.005) showing a value incremental over that of demographic, clinical and echocardiographic data (figure). In conclusions in idiopathic dilated cardiomyopathy, high OLF plasma levels are independent predictors of heart failure progression and adding incremental prognostic information to traditional parameters.



P2312 Prognostic value of cytokines and neurohumoral factors in congestive heart failure

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Background: Cytokines and neurohormones have been associated with poor prognosis in patients with congestive heart failure. On the other hand it has been shown that these factors are influenced by medical treatment.
Objectives: The aim of the study was to compare the prognostic value of cytokines and neurohumoral factors in patients with congestive heart failure under maximal uptitrated therapy with ACE Inhibitors.
Methods: We studied 100 patients with congestive heart failure (NYHA II or III), left ventricular ejection fraction <25% and treatment with enalapril 40mg/die, diuretics and digitalis. β-Blocker therapy was started in 91% of the patients during the follow up period. Serum levels of Interleukin-6, TNF-alpha, pro-ANP, ANP, proBNP, BNP, Noradrenalin, big- Endothelin were measured at inclusion of the study. Primary endpoint was death or heart transplantation. Secondary endpoint was defined as combined death, heart transplantation, worsening of heart failure or cardiac arrhythmias. Stepwise multivariate regression analyses were performed using 10 variables (Age, LVEF, bigET, Noa, ANP, proANP,BNP,proBNP, IL-6 and TNF alpha)
Results: During follow-up 39 patients died or had heart transplantation. 54 patients reached the combined secondary endpoint and 46 patient had no events. The mean follow up was 37 months (0.3-60months). A Cox proportional hazards regression analysis identified BNP as independant predictor for the primary endpoint. BNP was 236,4±249,76 fmol/l in patients without primary endpoint and 533,1±539.02 fmol/l inpatients who died or underwent heart transplantation. IL-6 had the strongest predictive value for the secondary endpoint. IL6 was 1.4±1.1 pg/ml in patients without an event and 3.6 ± 5.9 pg/ml in patients with events.
Conclusion: In the present study BNP is the strongest predictor for mortality or heart transplantation. But interleukin-6 is the most potent predictor for the combined end point of death, heart transplantation, worsening of heart failure or cardiac arrhythmias. A single measurement might help identifying patients at high risk of death or complications and should be monitored more closely.

P2313 Pre-trial severity of left ventricular dysfunction in heart failure determines outcomes: Val-HeFT echocardiography study

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Background: Earlier echocardiography (echo) studies indicated that left ventricular (LV) size and ejection fraction (EF) were predictors of mortality in heart failure (HF). The Val-HeFT (Valsartan in Heart Failure Trial) echo database from 5010 patients enabled evaluating the hypothesis that pre-trial severity of LV dysfunction determines morbidity and mortality.
Methods: Baseline LV internal diastolic diameter (LVIDd)and EF were grouped by quartiles (Q1-Q4): <6.3 to ≥7.5 cm and ≥32 to <22%, respectively. Risk ratios (RR) for morbidity (time to death or time to 1st of: sudden death with resuscitation, IV inotropic therapy, or hospitalization for HF), and mortality (time to death) were calculated from pooled data including valsartan and placebo patients using Cox regression analysis.

	Quartiles	% Morb.	RR vs Q4	P	% Mort.	RR vs Q4	P
LVIDd (cm)	Q1: <6.3	21.1	0.485	**	13.2	0.442	**
	Q2: 6.3 to <6.8	29.4	0.713	**	17.9	0.617	**
	Q3: 6.8 to <7.5	31.1	0.756	**	19.1	0.656	**
	Q4: ≥7.5	39.0	–	–	27.3	–	–
EF (%)	Q1: ≥32	22.6	0.506	**	13.9	0.501	**
	Q2: 27 to <32	29.6	0.687	**	19.1	0.706	**
	Q3: 22 to <27	30.7	0.711	**	19.8	0.725	*
	Q4: <22	40.2	–	–	26.4	–	–

*p=0.0002 **p<0.0001 (log-rank tests)

Results: Grouping the data according to severity of LV dilatation (increasing LVIDd) and systolic dysfunction (decreasing EF) demonstrated gradients of increasing morbidity and mortality at the higher baseline quartiles. RR between baseline quartiles showed the greatest reduction comparing the best (Q1) to the worst (Q4).
Conclusion: Val-HeFT echo data confirm that stratification of patients in HF by severity of increased LVIDd and decreased EF can identify patients most likely to suffer from morbidity and mortality.

P2314 Prognosis in severe heart failure due to Chagas' disease worse than heart failure due to idiopathic, ischaemic or hypertensive cardiomyopathy

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To evaluate clinical determinants of prognosis in a large hospital based series of outpatients with severe heart failure due to different etiologies, including Chagas' heart disease, we have followed up 1220 outpatients in a single Institution since 1991.

Patients were referred for treatment of heart failure in a tertiary care university hospital dedicated to cardiology, and followed-up for 25.6 ± 26 months. Patients' ages ranged between 13 and 72 (45.5 ± 11) years; 952 (78%) patients were men and 268 (22%) women. Heart failure was ascribed to idiopathic dilated cardiomyopathy in 454 (37.2%) patients. Etiologies were Chagas' heart disease in 242 (19.8%) patients, ischemic cardiomyopathy in 212 (17.4%), hypertensive cardiomyopathy in 170 (13.9%), and others in 142 (11.7%). Standard therapy included angiotensin converting enzyme inhibitors titrated to the patients' needs. Survival was assessed through Kaplan Meier method for each clinical variable categorized in terciles, to avoid pre-established categorizations. Subsequently, an univariate Cox proportional hazard model was fitted and multivariate analysis was performed, through pooled non-invasive clinical variables (non-invasive model), and cardiac catheterization variables (invasive model).

Results - 425 (34.8%) patients died in the follow-up, 74 (6.1%) patients underwent heart transplantation and 28 (2.3%) underwent other surgical interventions. In the non-invasive model, Chagas' heart disease etiology (relative risk of 2.72), left ventricular end diastolic diameter (relative risk 1.13) and left ventricular ejection fraction (relative risk 0.96) were identified as the main determinants of prognosis. In the invasive model, Chagas' heart disease etiology (relative risk of 9.13) and the cardiac index (relative risk 0.40) were identified as the most important determinants of prognosis.

Conclusion: In conclusion, prognosis in severe heart failure due to Chagas' disease was worse than prognosis in heart failure due to idiopathic, ischemic or hypertensive cardiomyopathy. In addition, Chagas' heart disease etiology surpassed other clinical markers of less favourable prognosis in this series.

P2315 Perioperative cardiac mortality rates in 109.904 surgical patients. A single-centre experience from 1991 to 2000

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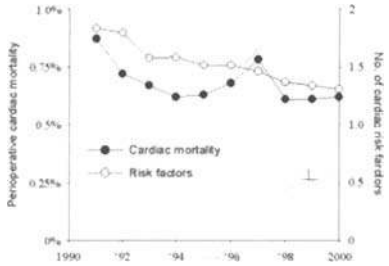
Aim: To assess the incidence of perioperative cardiac mortality in daily clinical practice; to identify risk factors; and to study changes over time.

Methods: A hospital database provided information on potential cardiac risk factors (age, gender, hypertension, smoking, angina, MI, heart failure, stroke, diabetes, preexistent renal failure and COPD), and perioperative mortality of all surgical admissions during 1991-2000. Risk factors were determined according to the ICD-9 coding system. The mortality cause was assessed by review of hospital records and autopsy results. Autopsy results were available in 33%. Patients admitted for cardiac surgery and patients under age 16 were excluded. Time trends were identified with chi-square tests and logistic regression analyses were applied to study the relation between risk factors and cardiac mortality.

Results: 109.904 patients underwent surgery. Overall perioperative mortality was 3.1%, and cardiac death 0.68% (22% of all-cause mortality). The incidence of cardiac mortality, and the prevalence of potential risk factors decreased with time (figure). Risk factors that were significantly associated with perioperative cardiac death were: previous MI (odds ratio [OR] 6.6; and 95% CI: 5.4-8.1); heart failure (OR 4.7; 3.9-5.7); renal failure (OR 3.3; 2.6-4.3); age >70 years (OR 3.1; 2.6-3.6); diabetes (OR 1.7; 1.3-2.1); male gender 1.4 (1.2-1.7); and hypertension (OR 1.3; 1.0-1.6). Angina, smoking, COPD, and hypercholesterolemia were not associated with increased cardiac mortality.



Cardiac mortality rates.

Conclusions: Although the incidence of perioperative cardiac death decreased during 1991-2000, patients with established coronary disease or preexistent renal failure still remain at high risk.

P2316 A non-invasive index to identify ambulant patients with chronic heart failure at increased risk of sudden death; results of UK-HEART

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Background: sudden death is common in patients with chronic heart failure (CHF). Patients with mild to moderate disease are at relatively greater risk of sudden death when compared to those with more severe functional impairment; identifying those at risk is an important goal. UK-HEART was designed to prospectively identify non-invasive predictors of mode of death in mild to moderate CHF.

Methods: between 1993 and 1995, 553 patients with stable mild to moderate CHF were recruited: 76% male, 63±10 (mean±sd) years old, 76% ischaemic heart disease, NYHA 2.3±0.5, EF 41.71±16.9%. Serum biochemistry, cardiothoracic ratio (CTR), echocardiographic and electrocardiographic variables, including QT and QRS dispersion (QTd and QRSd respectively) and heart rate variability and the presence of non-sustained ventricular tachycardia (NSVT) on 24 hour Holter monitoring were assessed. By 2000, after at least 5 years' follow-up, 201 patients had died, 67 (33%) suddenly.

Results: using the Cox proportional hazards regression model, CTR, QRSd, the presence of NSVT and QTd across the chest leads were found to be significant independent predictors of sudden death (all $p<0.04$). The hazard ratio (95% confidence intervals) represents the excess risk associated with the effect in parentheses. CTR (10% increase) 1.43(1.2-1.71); QRSd (10%increase) 1.11(1.04-1.19); NSVT (presence) 2.03(1.27-3.25); QTd (10%increase) 1.04(1.00-1.07).

An index was derived by summing weighted scores for each of the four variables (the 3 continuous variables dichotomized by their medians): CTR>0.52 (score 4), presence of NSVT (score 3), QRSd >42.7ms (score 2), QTd> 37ms (score 2), score 0 otherwise, total a maximum of 11. This index was found to perform well in identifying those at risk of sudden death. (SN-sensitivity, SP-specificity, PPV-positive predictive value, NPV-negative predictive value). For a score of 11: SN 98.5, SP 11.1, PPV 13.3, NPV 98.2; for a score of 0: SN 20.9, SP 95.9, PPV 41.2, NPV 89.8. The C statistic for the Receiver Operator Characteristic curve is 0.7.

Conclusion: an index derived from simple, readily measurable, non-invasive measures can be used to identify patients with mild/moderate heart failure at risk of sudden death.

HEART TRANSPLANTATION

P2317 Relation between left ventricular function and exercise tolerance in heart transplant recipients

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Background: Reduced post-transplant exercise tolerance is mainly attributed to the altered physiologic responses of denervated hearts to expercise. The contribution of left ventricular (LV) dysfunction is barely known. We assessed the left ventricular (LV) function and exercise tolerance in non-rejecting heart recipients, in connection with transplant coronary artery disease (TxCAD) and amount of interstitial fibrosis.
Methods: Echocardiographic analysis of LV function (M-mode-, 2D-, flow Doppler- and tissue Doppler) was performed in 120 patients (post-transplant time: 3 months -13 years), prior to exercise testing, cardiac catheterization and endomyocardial biopsy. Echocardiographic parameters were tested for relationships with histological, angiographical and exercise findings.
Results: Reduced percentage of predicted peak oxygen uptake was found in 117 patients (97.5%). Even without TxCAD, peak oxygen uptake reached only 73.8 ±9.2% of predicted values. The elevated LV end-diastolic pressure [LVEDP] (11.8 ±5.9mmHg) and reduced transmitral pressure half-time [PHT] (42.3 ±9.9ms) suggest, that without TxCAD, reduced exercise tolerance was mainly related to diastolic dysfunction. All TxCAD patients showed reduced exercise tolerance, which was highest in the angiographic TxCAD group. In patients with angiographic TxCAD, the LV ejection fraction, although lower than without TxCAD (p=0.0011), was in normal range (62.8 ±11.5%). The high LVEDP (14.8 ±5.6mmHg) and short PHT (30.1 ± 8.7ms) in these patients were indicative for a mainly diastolic dysfunction. The significantly reduced systolic wall motion peak velocities measured by tissue Doppler imaging in both TxCAD groups (angiographic and visible only by intracoronary ultrasound), suggests also the contribution of impaired systolic function to the exercise intolerance. Patients with TxCAD showed also reduced chronotropic responses to exercise ($p < 0.01$).
Impaired diastolic function and exercise intolerance appeared also related to interstitial fibrosis. Patients with diffuse perivascular and interstitial fibrosis showed higher LVEDP, shorter PHT and more altered exercise parameters than patients with minimal or reduced fibrosis ($p < 0.001$).
Conclusions: The LV diastolic dysfunction, closely related to interstitial fibrosis, is a major cause of post-transplant exercise intolerance. TxCAD impairs exercise capacity mainly by aggravating pre-existent diastolic dysfunction and reducing the chronotropic response to exercise. Post-transplant exercise intolerance is rarely the prime consequence of impaired LV systolic function.

P2318 Adenovirus-mediated gene transfer of interleukin-1 or RANTES antagonists prolongs heart allograft survival in a rat model

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Chemokines including RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted) play a key role in mediating leukocyte migration and activation within cardiac allografts, which represent crucial early pathophysiological events after engraftment. Other cytokines including interleukin-1 (IL-1) are also involved in the amplification of early leukocyte recruitment into the allograft. To prevent cellular infiltration and activation within the grafted heart, we have constructed recombinant adenoviral vectors expressing soluble IL-1 type II receptor (sIL-1RII), which antagonizes the IL-1 cytokine, and RANTES(9-68), which acts as an antagonist of RANTES.
Methods and Results: Heart allografts were performed in the F344/Lewis rat strain combination. Ex vivo gene transfer was carried out by intracoronary instillation of adenoviral vectors expressing sIL-1RII (2x10E10 plaque forming units; n = 10), RANTES(9-68) (n = 7), no transgene (n = 5) or saline solution with no virus (n = 6). Allograft survival was prolonged by sIL-1RII (15.6+5.7 days) and RANTES(9-68) (17.0+1.8 days) adenoviral vectors as compared to null-adenovirus (9.8+0.8 days; $p < 0.01$ for sIL-1RII and RANTES) or saline (9.8+2.1 days; $p < 0.01$ for sIL-1RII and RANTES). Immunohistochemical analysis will be presented.
Conclusions: Adenoviral vectors expressing IL-1 or RANTES antagonists may be a useful approach to prevent acute cardiac allograft rejection.

P2319 Role of B cells and macrophages in endomyocardial biopsies with ISHLT grade 0

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Purpose: Acute cellular rejection episodes are the main life threatening complications within the first year after heart transplantation [HTx]. This study tests the role of immunohistochemical evidence of B cells and macrophages in endomyocardial biopsies [EMB] without evidence of acute cellular rejection according to the Classification of the ISHLT.
Methods: Out of a total of 809 EMB with ISHLT grade 0 taken from 422 HTx patients (72 female, 350 male, mean age at HTx 46 years) with terminal heart failure (CAD=115, dCMP=274, others=33) 393 EMB without evidence of the Quilty phenomenon were divided into 5 time intervals [TI] after HTx (1st-4th month, N=70; 5th-12th month, N=48; >1st-2nd year, N=71; >2nd-4th year, N=78; >4th-10th year, N=126). In H&E stainings vascular reaction (endothelial cell swelling/vessel wall thickening) was graded and immunohistochemical reactions with antibodies directed against B cells (CD20cy, clone L26, Dako®) and macrophages (CD68, clone KP1, Dako®) were performed and evaluated semi-quantitatively by light microscopy (x200).
Results: 1. There was a positive reaction for B cells in 5.7% of EMB in TI I, in 14.6% in TI II, in 11.4% in TI III, in 11.8% in TI IV, and in 9.5% in TI V. 2. Immunohistochemical evidence of macrophages was found in 100.0% of EMB in TI I, in 93.7% in TI II, in 84.5% in TI III, in 83.3% in TI IV, and in 83.2% in TI V. 3. Distribution of positive reaction for B cells in males and females was as follows: male/female TI I 3.4/18.2%, TI II 11.9/33.3%, TI III 8.2/33.3%, TI IV 12.9/0.0%, TI V 11.1%/0.0%, and for macrophages: male/female TI I 100.0/100.0%, TI II 95.2/83.2%, TI III 83.9/88.9%, TI IV 83.3/83.3%, TI V 86.0%/66.7%. 4. There were no correlations between the immunohistochemical evidence of B cells and macrophages. 5. Severity of vascular reaction was independently of immunohistochemical evidence of B cells and macrophages.
Conclusions: 1. Evidence of activation of the humoral immunologic system and the unspecific immunologic system early after HTx is found in all HTx patients. 2. Evidence of humoral rejection is low in cases of absence of acute cellular rejection and increases within the 1st year after HTx. 3. Activation of the non-specific immunologic system plays a dominant role also in cases of absence of acute cellular rejection. 4. Activation of the humoral immunologic system during the first two years after HTx seems to be more pronounced in females. 5. Humoral immunologic reactions and non-specific immunologic reactions seem not to have an impact on the development of microvascular alterations after HTx.

P2320 Prognostic value of contrast stress echocardiography, myocardial stress scintigraphy and their combination in heart transplant recipients

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The diagnostic yield of dobutamine stress echocardiography (DSE) may be limited in heart transplant recipients (HTR) due to impaired image quality. As shown by our group, however, it can be improved by using both transpulmonary contrast agents and harmonic imaging. This study evaluates the prognostic value of contrast-DSE with harmonic imaging, of myocardial stress szintigraphy (SPECT) and of their combination.
Methods: 119 contrast-DSE and SPECT were performed in 81 HTR (66 male, aged 55±10,8 years) transplanted between 1985 and 1999. The contrast agent Optison® was injected intravenously as a bolus (0.3-1.0 ml) during rest and peak stress (dobutamine 5-40µg/kg/min). Regional wall motion was assessed offline by using the standard 16-segment model. SPECT was performed simultaneously (one day protocol) with application of the radiopharmacon (Tc99m-MIBI) at peak dobutamine stress. Any new or worsening wall motion or perfusion abnormalities were considered pathological.
Results: In 2 patients contrast-DSE, in 1 patient SPECT studies were not of diagnostic quality. No relevant side effects occurred. Within 12 months after the initial contrast-DSE 7 out of 23 patients with a pathological contrast DSE-result experienced cardiac events (6 x PTCA, 1x cardiac death; positive predictive value=PPV=30,4%) compared to 8 out of 50 patients with a pathological SPECT (7x PTCA, 1x cardiac death; PPV=16.0%). 7 out of 17 patients with both pathological contrast-DSE and pathological SPECT-results experienced cardiac events (6x PTCA, 1x cardiac death; PPV=41,2%). There was no siginificant difference between the negative predictive values for contrast-DSE, SPECT and their combination (95,7% vs. 95,4% vs. 96%, p= 0,68).
Conclusion: Contrast-DSE identifies patients with following cardiac events more precisely than SPECT, but the combination of both outmatches it. A normal contrast-DSE and/or SPECT appears to be a reliable marker for an eventless clinical course.

P2321 Mitochondrial permeability transition pore opening before cardiac graft acute rejection in rats

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We sought to determine whether mitochondrial permeability transition (MPT) pore opening might play a role in apoptosis during cardiac graft acute rejection. Seven to nine-week old male rats underwent an heterotopic (abdominal) cardiac transplantation that was either syngenic (Brown Norway/ Brown Norway, Syn group; n=10) or allogenic (Brown Norway/Lewis, Allo group; n=10). Transplanted hearts were harvested at day 3 or 5 following surgery. Mitochondria were isolated using differential centrifugations. Caspase 3 activity from the cytosolic fraction was assessed using a fluorimetric technique. Within the isolated mitochondria suspension, free Ca^{2+} concentration of the medium was measured by means of a specific microelectrode; MPT pore opening triggered by Ca^{2+} overload was defined as the brutal liberation of Ca^{2+} by the mitochondria. Cardiac graft rejection was evaluated using conventional histology grading. Acute rejection was detected in all Allo hearts at day 5, but was absent in Allo hearts at day 3. No rejection was detected in the Syn groups. At day 5, caspase 3 activity in Allo hearts averaged 41100 pmol/mg versus 3000 in the Syn hearts ($p<0.001$). At day 3, caspase 3 activity was normal in both Allo and Syn groups. The Ca^{2+} load that triggered MPT pore opening averaged 20 μM at day 5 in Allo versus 240μM in Syn ($p<0.001$). At day 3, Ca^{2+} load necessary to induce MPT pore opening averaged 240μM in Allo versus 320μM in Syn ($p<0.05$).

These data suggest an early sensitization to Ca^{2+} loading of the mitochondrial permeablity transition pore that occurs before the acute rejection and myocardial apoptosis following cardiac transplantation in the rat.

P2322 Long-term follow-up of combined heart and kidney transplantation. A single-center experience

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Irreversible renal dysfunction is considered to be a contraindication for heart transplantation. However simultaneous heart and kidney transplantation (HKT) can be an acceptable option for these patients.

Purpose: To assess our experience in simultaneous heart and kidney transplantation from the same donor with particular attention to long-term follow-up.

Methods: Retrospective analysis of medical records of 11 HKT patients who underwent combined HKT from the same donor from 1995 to 2000. The variables recorded were age, sex, etiology of cardiac and renal diseases, immunosuppressive protocol, ischaemic time of both allografts, and follow-up data in terms of number of rejection episodes of boths allografts, kidney function and survival.

Results: All HKT patients were males, being the average age of 53 $\pm$ 9,3 years. Donor's average age was 34 $\pm$ 9,39 years. Etiology of the cardiopathy was dilated cardiomyopathy 23%, ischemic 61% and retransplantation 15,4%. Etiology of nefropathy was: glomerulosclerosis 9%, Wegener 9%, nefrotoxicity 18%, nefroangiosclerosis 18% and unidentifyed 36%. Cardiac allograft ischemic time was 187 $\pm$ 95 min, kidney allograft ischemic time was 412 $\pm$ 97 min. Immunosuppressive regimen was cyclosporine, azathioprine and steroids in 1 patient and in the other 10 patients, cyclosporine, mofetil-micophenolate and steroids; average of cardiac rejections/patient: 0,4 $\pm$ 0,97. No rejections were identifyed in renal allograft. Average creatinine at 1, 2 and 4 years was: 1.3 $\pm$ 0,24, 1.1 $\pm$ 0,2, and 1,2 $\pm$ 02 mg/dl respectively. One patient (9%) died in the postoperative period due to bleeding related to renal allograft surgery. The remaining 10 patients are alive and asymptomatic after an average follow-up of 44,5 $\pm$ 17,2 months with normal function of boths allografts.

Conclusions: Simultaneous heart and kidney transplant from the same donor is a therapeutic aproach suitable for patients with terminal cardiac and renal diseases. Apart from perioperative mortality, the long-term evolution is good with high survival, low rate of cardiac rejection episodes, no renal rejection episodes and normal function of boths allografts.

P2323 Influence of prolonged left ventricular assist device support on post transplantation acute rejection and survival

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Although left ventricular assist devices (LVADs) can be life saving in deteriorating patients and offer opportunities for prospective HLA matching, they modulate the cell mediated and humeral immune systems. These changes can potentially influence both early and mid term outcome after transplantation (Tx). To clarify these issues we prospectively followed eleven patients from 1995 who had LVAD support and subsequently received transplants at our institution, consisting of 10 heart & 1 heart and kidney transplants. Nine were males & 2 were females. Ages ranged from 15-59 (mean 43.2) yrs. Original disease was ischaemic heart disease (IHD) in 8, dilated cardiomyopathy in 2 and congenital heart disease in 1. Duration of support was 4-23(mean 10.8) mths. Only one patient developed HLA class II antibodies following LVAD implantation. Of all the other patients who survived more than 3 months after LVAD over the same time period and were not transplanted, HLA antibody formation only occurred in 1(4.5%) of 22. Prospective HLA matching was done in all patients and in 2 a 0DR and in 4 a 1DR mismatch was achieved. Pre-operative cross match was negative in all. There were no early deaths and two late deaths, one at 4 months due to donor heart dysfunction thought to be due to pre-existing donor hypertension and one at 6 years 3 months due to neurological disease predating transplantation. Follow up was up to 6 yrs 3 mths after Tx. The actuarial survival for the group was 88.9% at 1 and 88.9% at 5 yrs compared to 82.7% and 78.8% in the 256 non LVAD patients transplanted over the same time period. All 9 survivors are in NYHA Class I at latest follow up. There was a tendancy to lower rejection in this group. Angiographic follow up showed minimal disease in two patients. In conclusion this limited study has shown that LVADs are associated with no significant incidence of HLA antibody formation, possibly a low incidence of acute rejection presumably due to the reported apoptosis of T cells, may allow for prospective HLA matching and the mid term results are excellent.

P2324 Usefulness of plasmapheresis in the management of severe allograft dysfunction without cellular rejection after heart transplantation

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Severe allograft dysfunction without signs of cellular rejection on endomyocardial biopsy (EMB) is a major complication after heart trans-plantation (HT). The anatomopathologic diagnosis and treatment of this kind of rejection (also called humoral rejection) are a matter of debate, but it is generally considered to be mediated by antibodies and is more dangerous than cellular rejection. The treatment used in our centre for this complication consists of a steroid bolus, cyclophosphamide or mofetil mycophenolate, and plasma-pheresis

The aim is to assess the incidence of severe HT allograft dysfunction without EMB evidence of cellular rejection, and the effectiveness of our management protocol.

Methods: Retrospective analysis of medical records of HT patients who had severe allograft dysfunction (ejection fraction < 30% and need of i.v. inotropic support and/or intraaortic baloon pumping). Clinical suspicion of humoral rejection was required upon observation of severe allograft dysfunction and no lymphocytic infiltrates in EMB tissue. The variables recorded were age, sex, time post-HT of immunofluorescence (IF) studies of EMB tissue, number of plasmapheresis sessions, and follow-up data on allograft function and survival.

Results: Of a total of 386 HT patients, 12 patients (3.1%) gave rise to clinical suspicion of humoral rejection (11 males, mean age 55.0 $\pm$ 8.3 years). Time to onset after HT was 16.7 $\pm$ 21.8 months (range 2-72). The IF studies (C3, C4, c1q, fibrin, IgG, IgM and IgA) were mainly negative. The number of plasmapheresis sessions was 10.0 $\pm$ 3.9 (range 7-19). Evolution was satisfactory in 11 of the 12 patients (91.6%), who regained normal allograft function and were in NYHA functional class I after a mean follow-up period of 36 $\pm$ 18 months. Two of these patients died (after 24 and 36 months) from non-cardiac cause (abdominal aortic aneurism surgery and lower ischaemia surgery, respectively). The only patient who did not improve underwent heart retrans-plantation 3 months after detection of humoral rejection. Plasmapheresis gave rise to no serious complications.

Conclusions: Severe allograft dysfunction after HT without signs of cellular rejection on EMB is an infrequent but major complication. Our management protocol, which includes plasmapheresis, has generally been successful, allowing total recovery of allograft function in 90% of cases. Anatomopathologic diagnosis needs to be improved.

DIASTOLIC FUNCTION IN HEART FAILURE

P2325 Effect of atrial fibrillation on Doppler indexes of left ventricular diastolic function

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Doppler transmitral (M) and pulmonary vein (PV) flow velocity curves are generally used to describe left ventricular diastolic function. However, these indexes are dependent on several factors and are only defined for patients in sinus rhythm (SR). Atrial fibrillation (AF) is a common arrhythmia characterized by a lack of organized atrial mechanical activity and, thus, has a confounding influence on Doppler indexes. AF is often a consequence of diastolic dysfunction and both conditions frequently coexist making it difficult to assess the true effect of AF on Doppler indexes. Therefore, we have chosen the experimental approach to measure Doppler indexes first in SR and subsequently after induction of AF in 10 patients (6 men, 4 women, mean age 53±8 years) undergoing radiofrequency ablation of paroxysmal AF (circular insulation of PV). Four patients had a history of hypertension with mild left ventricular hypertrophy. Otherwise, none had signs of structural heart disease and everyone had normal or near normal diastolic function by Doppler echocardiography. Multiplane transesophageal echocardiography was performed in patients under general anesthesia at the beginning of the procedure to measure Doppler M (sample volume between leaflet tips) and left upper PV (sample volume 1 to 2 cm within the orifice) flow velocity curves. Measurements were first obtained in SR and during right atrial pacing (RAP) at 60, 80, and 100 ppm. AF was then successfully induced in all patients by high rate pacing (cycle length 140 to 180 ms) in the coronary sinus and measurements were repeated. Each patient served as his own control. Statistical analysis (paired t-test) was performed between measurements in AF and SR/RAP at comparable heart rates. Data shown in the table are mean±SD.

	HR (/min)	E-wave (cm/s)	A-wave (cm/s)	DT (ms)	PV TVI syst./diast.	PV Vmax syst./diast.
SR/RAP	78±10	57.3±19.1	46.6±20.9	256±29	1.17±0.26	1.61±0.87
AF	76±7	65.5±22.7		213±29	0.69±0.23	0.63±0.26
p	NS	<0.05		<0.01	<0.001	<0.01

HR = heart rate; DT = deceleration time; TVI = time velocity integral; Vmax = peak velocity

In summary, keeping other factors constant, AF by itself shortens deceleration time and decreases syst./diast. pulmonary flow ratios. These data may serve to define a "normal" range of Doppler indexes for patients in AF.

P2326 Is left ventricular dysfunction related to carotid atherosclerosis in hypertensives?

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This study has been designed to investigate the relationship between carotid atherosclerosis and diastolic dysfunction in hypertensives. The study population includes 142 hypertensive (HT) patients (64 females and 78 males) selected from a data base consisting of 3541 subjects who were referred to our ultrasound cardiovascular laboratory in the last five years (1995-2000) at the first diagnosis of mild to moderate (according to the WHO/ISH criteria) essential hypertension, younger than 55 years. Accurate evaluation of wall carotid artery and left ventricular function and structure were the main inclusion criteria. From the analysis were excluded all the subjects with other associate major cardiovascular risk factors. Examination of both common carotid arteries was detected by high-resolution vascular ultrasound to evaluate carotid Intima-Media Thickness (IMT) and M-B mode and Doppler ultrasonography examination was performed to evaluate left ventricular structure and function. Left ventricular diastolic filling was detected by peak early LV filling velocity/peak atrial filling velocity (E/A), deceleration time (DTE) and isovolumic relaxation time (IVRT). According to carotid IMT values all patients were sub-grouped as follows: group A consisting of 85 (59.9%) pts with IMT > 1 mm; group B consisting of 57 (40.1%) pts with carotid IMT < 1mm. Our results shows that IVRT, DTE and RWT were significantly ($p < 0.05$) higher in group A (IVRT 106 + 15.5 ms; DTE 237 + 51.3 ms; RWT 0.40 + 0.08) than in group B (IVRT 97.54 + 13.1 ms; DTE 203.3 + 27 ms; RWT 0.37 + 0.06). The prevalence of LVH was significantly ($p< 0.01$) higher in-group A (30/85; 35%) than in-group B (8/57; 14%). In all subjects with normal left ventricular geometry a positive correlation ($r = 0.33$; $p< 0.04$) between IMT and DTE was observed. The main new finding of the present study is the recognition of an association between higher levels of carotid arterial wall thickness and left ventricular diastolic dysfunction in newly diagnosed essential hypertensives. This association seems to be independent by the presence of left ventricular hypertrophy. These results are consistent with the indication that the evaluation of carotid wall morphology has to be recommended not only in hypertensive patients with LVH but also in those with alterations in left ventricular diastolic function. This approach might improve the prognostic stratification of hypertensive subjects and it might be suitable to recognize subset of patients at higher risk of cardiovascular disease or events.

P2327 Recruitment into a diastolic heart failure study – Few patients meet the criteria

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Purpose: The Hong Kong Diastolic Heart Failure Study (HKDHF study) which started in 1999 is a multicentre trial comparing diuretic alone, diuretic plus ramipril or diuretic plus Irbesartan in patients with diastolic heart failure (DHF) on quality of life (QOL), exercise capacity, hospitalizations and mortality. Recruitment has been slow. We have investigated the reasons why.
Methods: The main inclusion criteria are: clinical History of heart failure within 2 months prior to screening including a chest X-ray demonstrating pulmonary congestion; NYHA Functional Class II - IV; left ventricular ejection fraction > 45% by echocardiography (M-mode/2D/AVP) or a radionucleotide technique and therapy with diuretics with stable dose > 14 days prior to the screening. After stabilization patients are randomized into one of the 3 treatment arms. A QOL questionnaire, 6min walk test, echocardiography and natruiretic peptides are measured at baseline, 3, 6 and 12 months.
Results: In the first 14 months 1400 subjects with a history of heart failure were screened in our centre (PWH). 847 were women and the average age was 77.5 yrs and 72.6 yrs for men (553). All had an echocardiogram. Of these 40 subjects (2.86%) were recruited into the study (currently 90). There were many reasons for rejection including administrative 102 (7.3%), CRF 217 (15.5%), Valvular HD 152 (10.9%), Haematology/other blood abnormality 228 (16.3), MI and/or long term ACEI 407 (29.1%), Dementia 40 (2.9%), Other medical reason 216 (15.4%)EF ≤ 45%, 16 (15.4%), Unstable angina 23 (1.6%), COAD (not HF) 16 (1.1%), Chest infection (not CHF) 9 (0.6%),Very ill 63 (4.5%), Frail 53 (3.8%), and Died before randomization 16 (1.1%).
Conclusions: Our experience indicates that a large scale DHF study will be difficult to conduct as many patients with DHF are very elderly, have significant co-morbidities, and many others do not have DHF on further investigation.

P2328 Reliability of exponential versus four-parametric logistic time constant estimated from different ventricular isovolumic pressure fall intervals

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In left ventricular pressure (LVP) curves, the cut-off points of the isovolumic period are not clearly identified. A reliable method to estimate the time constant (tau) of this pressure fall has therefore to be robust against choosing different regression interval limits. This property was tested in the four-parametric logistic model P=Pinf+(P0-Pinf)/[g+(1-g)exp(t/tau)] and in the usual three-parametric exponential model (i.e. P with fixed g=0).
LVP curves were obtained from 36 isolated ejecting hearts (each 12 from rats, guinea pigs, and ferrets), working in an artificial circulation apparatus. Standard isovolumic pressure fall intervals (IPI) were taken from peak -dP/dt to the re-encountered end-diastolic pressure of the preceding beat. The start-point was then varied by ±5ms in ms-steps, thus forming 11 different IPI from which median tau and mean deviation from that median (MDM) were calculated by both of the compared models. This procedure was repeated by varying the end-point of IPI. The differences in MDM between exponential and logistic model were tested by Wilcoxon matched pair signed rank tests.
No species differences were notable; the results depend only on the actual logistic shape parameter, g (Table). By numerical reasons, g=0 turns the logistic model into the exponential, and the latter is numerically favorable at small g. However, most hearts present (a posteriori) with considerable g>0, where the logistic model is significantly more robust against IPI range changes.

Variability of time constant estimates

Subset	N	variable	ExpMED	ExpMDM	LogMED	LogMDM	Advantage Exp/Log	Wilcoxon
g<0.45	18	startpoint	24.5	0.7	16.5	2.2	12/6	p<0.01
		endpoint	23.9	0.6	15.4	2.1	15/3	p<0.01
g>0.45	18	startpoint	22.1	1.1	14.1	0.3	3/15	p<0.01
		endpoint	22.1	0.4	14.3	0.1	3/15	p<0.05

variable: variation of start- or end-point of IPI, respectively; Exp: 3-parametric exponential, Log: 4-parametric logistic model; MED: median time constant (ms); MDM: mean deviation from median (ms); Advantage: number of less MDM in exponential and in logistic fit, respectively.

In conclusion, the exponentially estimated tau is not only biased by model violation but significant additional error is caused by errors in determining the IPI; both disadvantages are overcome by the four-parametric logistic model.
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P2329 Independent and additional prognostic value of left atrial enlargement in the elderly with dilated cardiomyopathy

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Previous studies have shown that abnormal mitral flow patterns and left atrial (LA) enlargement are independently associated with survival in patients with left ventricular (LV) dysfunction. However, it is not known whether these outcome indicators can provide different information in patients of various age groups.

This study was designed to assess the prognostic value of restrictive mitral flow pattern (RMFP) and increased LA size in older and younger patients with LV dysfunction.

A series of 207 patients consecutively examined at our Doppler-echocardiographic laboratory and diagnosed with LV dysfunction (ejection fraction <45%) due to either ischemic or idiopathic dilated cardiomyopathy (DCM) was evaluated at the index Doppler echocardiogram. Patients were grouped into those ≤70 years (n=102; mean age: 61 years) and those >70 years (n=105; mean age: 78 years). All patients were subsequently followed-up for a mean period of 22±14 months.

In patients >70 years, indexed LA size (>26 mm/m^2) was the single best predictor of the fatal outcome (hazard ratio [HR]: 3.0, p=0.018) and emerged as the most important outcome variable of the combined end point (HR: 2.2, p=0.016) on multivariate analyses. In patients ≤70 years, RMFP, characterized by an early wave deceleration time (EDT) <140 msec, was independently associated with cardiac death or heart failure hospitalization (HR: 5.7, p=0.0013). When, demographics, clinical, echocardiographic and Doppler measures were analyzed in hierarchic order, indexed LA size yielded the most valuable contribution in predicting the combined end point in older patients (global chi-square from 11.5 to 18.7). RMFP was associated with the higher additional prognostic value in younger patients (global chi-square from 14.4 to 24.1).

Increased indexed LA size had an independent and incremental prognostic value in patients aged >70 years with LV systolic dysfunction due to either ischemic or idiopathic DCM. Although RMFP can predict cardiac death and events in younger DCM patients, the more frequent blunting of early mitral flow and EDT prolongation with advancing age may decrease its value in the elderly. The prognostic relevance of LA enlargement is likely to descend from the impact of concomitant increases in LV filling pressure as well as significant mitral regurgitation.

P2330 Anti-G garment inflation: a suitable method to increase pulmonary capillary wedge pressure in healthy elderly subjects

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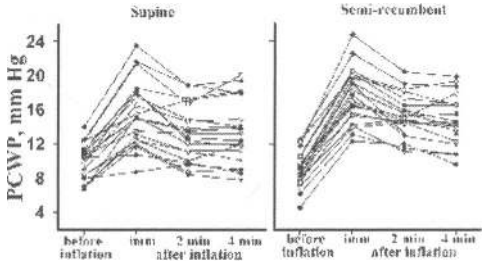
Background: Non-invasive assessment of pulmonary capillary wedge pressure (PCWP) could facilitate treatment of heart failure in the elderly. Therefore, we want to study whether changes in PCWP can be assessed using the blood pressure (BP) response to the Valsalva maneuver. Initially, we investigated whether inflation of an anti-G garment was a suitable non-invasive method to increase PCWP temporarily in healthy elderly subjects.

Methods: In 20 subjects, before, immediately after, and at 2 and 4 minutes after anti-G garment inflation to 52 mmHg (1 psi), PCWP and continuous cardiac output (CCO) were measured with a CCO Swan-Ganz catheter and BP and heart rate with Finapres®, in supine and semi-recumbent position.



Results: The figure shows individual PCWP values. Immediately (imm) after inflation, group mean PCWP (mmHg±SD) increased from 9.9±2.1 to 15.5±3.9* in supine and from 8.9±2.0 to17.5±3.3* in semi-recumbent position (* p<0.01 vs. before inflation, paired t-test). After 4 minutes, PCWP was still significantly elevated. Cardiac output and heart rate did not change after inflation; mean BP slightly increased.

Conclusion: In healthy elderly subjects, anti-G garment inflation is a safe, non-invasive, method to induce an increase of PCWP in supine and semi-recumbent position. Our findings justify its application in future studies in which non-invasive temporary increase of PCWP is required.

P2331 Evaluation of post haemodialysis changes in left ventricular diastolic function by standard and load-independent echocardiographic parameters

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Background: Tissue Doppler imaging of the lateral mitral annulus (TDI) and intraventricular M-mode color inflow Doppler (Vp) have been described as theoretically load-independent indexes of left ventricular relaxation, while transmitral and pulmonary venous flows are strictly load dependent. Hemodialysis (HD) session in chronic renal failure patients leads to acute and significant left ventricular pre and after load changes.

Aim of the study: To evaluate the effective load indipendence of TDI and Vp.

Methods: Thirteen patients without history of heart disease, ECG changes or hypertension (7 male, age: 53±12 yrs, creatinine: 9.7±0.9 mg/dl, mean duration of dialitic treatment: 7.6±6.2 yrs, mean weight loss after HD: 2.8±0.6 Kg, duration of HD session: 4 hours) have been evaluated before (<30 min, PreD) and after (<30 min, PostD) HD. The following parameters have been evaluated: Left ventricular ejection fraction (EF), early diastolic transmitral flow velocity (E) and its deceleration time (DT), late diastolic transmitral flow velocity (A) and its duration (DA), Systolic (X) and diastolic (Y) pulmonary flow velocities and duration of the reverse pulmonary flow wave (DZ), iso-volumic relaxation time (IVRT), early (Ea) and late (Aa) diastolic TDI velocities and Vp calculated as the slope of the first aliasing of the proto diastolic left ventricular filling measured from the mitral plane to 4 cm into the left ventricle.

Results: Heart rate changed from 78±12 to 85±11 bpm (ns); the EF from 57±9 to 58±5% (ns). Changes of diastolic parameters are reported in the table.

	E cm/s	A cm/s	DT msec	Dz-Da msec	IVRT msec	X cm/s	Y cm/s	E' cm/s	A' cm/s	Vp cm/s^2
PreD	67(14)	84(15)	227(51)	-52(36)	84(17)	49(12)	35(5)	13(4)	15(3)	60(15)
PostD	56(16)	81(25)	195(58)	-28(30)	87(12)	49(17)	39(8)	12(5)	14(3)	65(20)
	p<.05	ns	p<.05	p<.05	ns	ns	ns	ns	ns	ns

Conclusions: TDI and Vp seems to be independent from load changes due to HD treatment. The independence of TDI and Vp from load conditions support their use in the left ventricular diastolic functional evaluation as a more reliable alternative to transmitral and pulmonary venous flow Doppler parameters.

P2332 Response of the restrictive left ventricle diastolic filling to Valsalva manoeuvre is predictor of events in patients with systolic dysfunction

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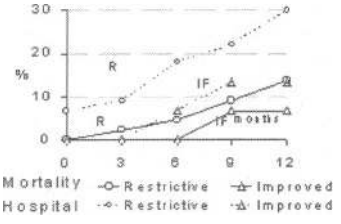
The aim was to evaluate the prognostic value of the response of restrictive transmitral inflow pattern to standardized Valsalva manoeuvre, in patients with advanced left ventricle systolic dysfunction.

Methods Fifty nine patients with ischemic and dilated cardiomyopathy and EF<30% (mean 23±3), who showed restrictive left ventricle diastolic filling pattern (E/A >2, DT <150 msec), and had no evidence of mitral regurgitation greater than mild degree on Doppler assessment, were investigated. Mitral inflow velocities were recorded with sample volume positioned at the leaflet tips, first at the end of normal expiration and then during the strain phase of standarized Valsalva manoeuvre.



Results In 44 (75%) patients Valsalva manoeuvre induced decrease of both E and A velocity during straining phase, but the restrictive left ventricle diastolic filling pattern remained unchanged (Restrictive pattern). In the remaining 15 (25%) patients E velocity was decreased and A velocity was either increased (12 patients) or slightly decreased (3 patients) and diastolic filling pattern was changed (E/A<2) and pseudonormalized (improved filling pattern). Patients were followed up for 12.1±4.1 months. In patients who showed no reversion of the restrictive filling pattern during Valsalva manoeuvre there were 6 deaths (13.6%) and 13 hospitalization (30%) on account of heart failure worsening. In patients who showed improvement of the diastolic filling pattern there were 1 death (6.7%, NS) and only 2 hospitalization (13,3% P< 0.05).

Conclusion Restrictive filling pattern represents advanced left ventricular diastolic dysfunction. Unimprovement of the filling pattern in response to preload reduction by Valsalva manoeuvre can detect patients with more adverse outcome.

P2333 Role of hypoalbuminemia in pulmonary oedema associated with diastolic heart failure

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The main cause of pulmonary edema is a decrease in the gradient: serum colloid osmotic pressure (COP) - pulmonary artery wedge pressure (PAWP). The respective contributions of COP and PAWP abnormalities in pulmonary edema resulting from diastolic heart failure have not been previously evaluated. Therefore we measured COP and PAWP in 34 controls, in 26 pts with pulmonary edema and systolic heart failure (LVEF<50%: SHF) and in 37 pts with pulmonary edema and diastolic heart failure (LVEF>50%: DHF).

Methods: COP was estimated from albuminemia and protidemia. PAWP was estimated within the first hours following admission using Doppler-echocardiography, from isovolumetric relaxation time (IRT) and mitral flow propagation velocity with color M mode (Vp): PAWP= 4.5x 1000/(2xIRT+Vp)-9.

Results: Patients with DHF were older than pts with SHF (82±8 versus 75±14 years) and have more frequently marked hypoalbuminemia <30g/l (68% versus 38%, p<0.01).

	Albuminemia(g/l)	COP (mmHg)	PAWP (mmHg)	COP-PAWP
controls	35.1±5	25±3.7	11.1±2.5	13.6±5
SHF	31.1±5*	23.6±4	25.3±4*	-1.2±6*
DHF	24.9±7*°	19.7±5*°	19.6±8*°	0.0±6*

*p<0.01 DHF or SHF versus controls; °p<0.01 DHF versus SHF

Conclusions: PAWP was lower in DHF than in SHF. However the gradient COP-PAWP was similar in DHF and SHF since COP was lower in DHF. Thus our results suggest that low albuminemia (resulting in low COP) is a major determinant of pulmonary edema in patients with DHF.

PATHOPHYSIOLOGY OF HYPERTENSION

P2334 Hypertensive subjects with "non-dipping" circadian blood pressure profile have reduced baroreflex sensitivity

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Purpose: Subjects with attenuated or even absent nighttime blood pressure (BP) fall are at higher risk of hypertensive organ damage. The factors responsible for nocturnal BP decrease are not fully understood. An impairment of autonomic cardiovascular regulations has been suggested. The aim of study was to compare indices of baroreflex sensitivity and heart rate variability between hypertensive subjects with preserved (dippers) or absent (non-dippers) night BP fall.

Methods: The study investigated 121 hypertensive patients (61 essential hypertension, 37 primary aldosteronism, 7 pheochromocytoma, 16 undetermined). Ambulatory blood pressure monitoring (SpaceLabs 90207) was performed after washout from chronic medication (alfa and/or Ca blockers allowed only). Time-domain indices of heart rate variability (mean NN, SDNN, rMSSD) and baroreflex sensitivity (BRS) were assessed by cross-spectral analysis of simultaneous recordings of RR intervals (ECG) and continuous finger arterial pressure (Finapres) during spontaneous (SR, 5-min) and controlled respiration (CR, 3-min, 0.1 Hz). Non-dippers were defined as subjects with nighttime (22-06h) systolic and diastolic BP fall < 10% of average daytime (06-22h) BP.

Results: Dippers and non-dippers differed in age, mean 24h systolic and diastolic BP, and in baroreflex sensitivity. There was no difference in etiology or duration of hypertension, casual BP, body mass index, and time-domain indices of heart rate variability (see table).

Characteristics of dippers/non-dippers

Variable	Non-dippers (n=63)	Dippers (n=37)	p value (t-test)
Age (years)	49.0 ± 10.5	42.5 ± 11.7	0.005
24h SBP (mmHg)	148 ± 17.4	138 ± 22.4	0.014
24h DBP (mmHg)	94.3 ± 11.3	85.5 ± 14.4	0.001
Mean NN-SR (ms)	944 ± 129	932 ± 154	0.67
SDNN-SR (ms)	41.3 ± 19.4	49.6 ± 33.9	0.12
rMSSD-SR (ms)	27.8 ± 19.0	35.7 ± 29.2	0.11
BRS-CR (ms/mmHg)	10.9 ± 6.5	15.4 ± 11.1	0.014

Values are means ± SD.

Conclusions: Time-domain indices of heart rate variability are not significantly altered in non-dippers. The absence of sufficient nighttime BP decline is associated with reduced baroreflex sensitivity.

P2335 Nighttime blood pressure variability as a predictor of diurnal blood pressure pattern stability

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Objective: Detailed assessment of diurnal BP pattern stability.

Materials and Methods: Stability of diurnal BP pattern was analyzed on 48 h ABPM in 80 pts (27 men and 53 women, mean age 54,9+1,6 years). ABPM was performed in the hospital to provide standard daily activity of the pts during the both days of investigation. Pts with sleep disturbances during at least one night of the investigation were not included into analysis.

Results: According to diurnal index (DI) of systolic BP (SBP) as traditional criteria for BP diurnal pattern assessment (dippers or non-dippers) stable BP diurnal rhythm was observed in 75% pts (36% were stable dippers, 39% - stable non-dippers). In 25% pts diurnal BP pattern transformed during the second day of ABPM: in 9% pts from dipper to non-dipper, in 16% - from non-dipper to dipper. Due to wide intraindividual DI variations we tried to provide quantitative assessment of diurnal BP pattern stability. Using standard deviation (SD) of DI during the 1st and the 2nd day of ABMP the pts were divided to tertiles with cut off points 2,4 and 4,9. Highly stable diurnal BP rhythm (SD DI 0–2,4) was revealed in 44% pts, moderately stable (SD DI 2,5–4,9) - in 30%, unstable (SD DI >5%) – in 26%. When traditional criteria were used the groups were highly heterogeneous on nighttime BP variability but there was no significant difference between the group mean values. When quantitative assessment of diurnal BP pattern stability pts with unstable rhythm had the highest nighttime BP variability.

Diurnal BP pattern	SD nighttime SBP, mm Hg	SD nighttime DBP, mm Hg
Traditional criteria		
Stable dippers	6,03±0,74	3,89±0,54
Dippers-non-dippers	7,15±1,52	3,58±0,55
Non-dippers - dippers	7,27±2,76	4,50±1,72
Stable non-dippers	8,65±1,44	5,08±0,70
Quantitative criteria		
Highly stable	5,05±0,79	3,61±0,49
Moderately stable	5,82±0,87	3,54±0,42
Unstable	11,99±1,56*	6,15±0,87*

*p<0,05 to compare with both other groups

Conclusion: New quantitative criteria allowed to assess BP diurnal pattern stability more precisely than tradition ones. High nighttime BP variability may be a predictor of diurnal BP pattern unstability.

P2336 Ambulatory blood pressure load can predict arterial pressure waveform contour in patients with essential hypertension

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The magnitude and timing of wave reflections are major determinants of the arterial pressure wave (APW) contours. Whether the different components of the overall blood pressure (BP) load affect the APW shape in essential hypertension has not been well defined.

Methods: To assess this, in 104 untreated, newly diagnosed with stage I-II (JNC VI) essential hypertension patients (pts) (aged 54±10 years, office BP 154/97 mmHg), echocardiography and ambulatory 24-hour blood pressure (ABP) monitoring was performed. APW was recorded by carotid applanation tonometry and waveform shape was expressed by the augmentation index (AI) according to Murgo et al classification.

Results: In the entire study population, LVMI was 92 gr/m^2, RWT was 0.48, 24h-SBP was 137mmHg, 24h-DBP was 85 mmHg and AI was 0.11±0.25. Patients with with a dominant late systolic peak (62 pts, AI=0.16±0.2) compared to those with a dominant early systolic peak (42 pts, AI =-0.002±0.4) were older (49 vs 56 years) and had significantly increased LVMI (98 vs 82 gr/m^2), RWT (0.49 vs 0.45), 24h-SBP (140 vs 129 mmHg), 24h-DBP (87 vs 80 mmHg), 24h ambulatory pulse pressure (PP) (53 vs 48 mmHg), daytime SBP (142 vs 132 mmHg), daytime DBP (90 vs 84 mmHg), nighttime SBP (129 vs 120 mmHg), nighttime DBP (78 vs 72 mmHg), 24h systolic load (43% vs 24%) and 24h diastolic load (38% vs 28%). AI was positively correlated with age (r=0.38, p<0.05), office SBP (r=0.21, p<0.05), LVMI (r=0.44, p<0.001), 24h-SBP (r=0.33, p<0.05), 24h-DBP (r=0.24, p<0.05), 24h ambulatory PP(r=0.24, p<0.005) and 24h-SBP and DBP load (r=0.27, p<0.05 and r=0.0.23, p<0.05 respectively). For the pooled population, in a multivariate model including office BP and ABP parameters, only the daytime SBP was identified as an independent determinant of AI (beta=0.45, p<0.001).

Conclusion: Among the different components of the overall hypertensive burden, daytime SBP affects APW contour to a greater extent in pts with moderate essential hypertension.

P2337 Effect of the breathing pattern on autonomic cardiovascular function in Andean high-altitude natives with and without chronic mountain sickness

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We evaluated the hypothesis that subjects with polycythemia and chronic mountain sickness (CMS) suffer from an impaired autonomic cardiovascular regulation, and tested the effect of different breathing patterns on arterial oxygen saturation (SaO2) and autonomic function.
Ten Andean natives with a hematocrit (Hct) >65%, and 10 natives with an Hct <55%, all living permanently at an altitude of 4300 m, were included into the study. Cardiovascular autonomic regulation was evaluated by spectral analysis of hemodynamic parameters and by computation of the spontaneous baroreflex sensitivity, while subjects breathed spontaneously or frequency-controlled at 6 or 15 breaths/min, respectively. The recordings were repeated after a one-hour administration of supplemental oxygen and after performing breathing at 6 breaths/min for one hour, respectively.
Subjects with Hct >65% showed an increased incidence of CMS compared to subjects with Hct <55%. Spontaneous baroreflex sensitivity was decreased in subjects with high Hct compared to the control group (repeated measurements at 2 subsequent days: 3.9 ± 2.1 and 5.9 ± 2.2 ms/mm Hg vs. 11.2 ± 8.5 and 11.1 ± 5.5 ms/mm Hg, $p<0.05$ between groups). The effects of supplemental oxygen or modification of the breathing pattern were: 1) Ventilation and SaO2 was significantly increased in all subjects after the administration of oxygen. 2) Blood pressure and heart rate decreased significantly after both maneuvers in both groups. 3) Baroreflex sensitivity increased significantly in subjects with high Hct and was not different from subjects with low Hct after administration of oxygen as well as after low-frequency breathing.
Temporary slow-frequency breathing provides a beneficial effect on the autonomic cardiovascular function in high-altitude natives with polycythemia and CMS.

P2338 Baroreflex sensitivity in normotensive subjects with a family history of hypertension: effect of tilting

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Developed hypertension is characterized by decreased baroreflex sensitivity. It is not completely clear whether changes in the baroreflex sensitivity precede hypertension development or they are secondary to high blood pressure. That is why we studied the baroreflex sensitivity at the pre-hypertensive stage of hypertension development.
Methods: Blood pressure and heart rate were monitored by finapres device in 59 normotensive subjects with a family history of hypertension (28.6 ± 0.5 years) and 46 normotensives without a family history of hypertension (25.7 ± 0.7 years). The baroreflex sensitivity was estimated by the sequence method in supine position and in consecutive half-a-minute intervals during ten-minute up-right tilting (65°). Multiple regression model was built with the baroreflex sensitivity in supine position as a dependent variable.
Results: In heart rate and diastolic pressure we did not find any significant differences between the two groups. Systolic blood pressure was significantly higher ($p = 0.011$) and baroreflex sensitivity in supine position significantly decreased ($p = 0.008$) in normotensives with a family history of hypertension as compared to those without a family history of hypertension. During the first and the second half-a-minute interval of up-right tilting the baroreflex sensitivity was also significantly decreased in normotensives with a family history of hypertension comparing to the subjects without a family history of hypertension ($p = 0.001$ and $p = 0.01$, respectively). During remaining half-a-minute intervals of ten-minute tilting the baroreflex sensitivity was not significantly different between the two groups. Multiple regression model showed that the baroreflex sensitivity in supine position was significantly influenced by heart rate ($p < 0.0001$), age ($p = 0.0016$) and a family history of hypertension ($p = 0.0367$).
Conclusions: We proved altered baroreflex sensitivity even in normotensive subjects with a family history of hypertension, what could be one of the earliest changes in essential hypertension development.

P2339 Plasma level of atrial and brain natriuretic peptide and left ventricular geometry in patients with essential hypertension

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Natriuretic peptides, atrial (ANP) and brain (BNP) are known to be elevated in hypertensive patients (pts), especially in those with left ventricular hypertrophy and dysfunction, but their relation to different patterns of left ventricular geometry (LVG) is not clearly established.
The aim of the study was to estimate relation between plasma ANP and BNP levels and patterns of LVG in pts with hypertension.
Material and methods: Studied group consisted of 80 pts (37 males, 43 females) aged 52.5±12.6 yrs with mild, moderate and severe essential hypertension. Subjects with other diseases affecting structure and function of the heart were excluded. As control group (CG) served 19 healthy subjects aged 50.5±9.6 yrs In every patient plasma levels of ANP and BNP were estimated by radioimmunoassay and echocardiographic study was performed. According to echocardiographic measurements every patient was classified into one of four patterns of LVG: normal geometry (NG), concentric remodeling (CR), eccentric hypertrophy (EH) and concentric hypertrophy (CH).
Results: (table)

	CG (n = 19)	NG (n= 18)	CR (n = 21)	EH (n = 17)	CH (n = 24)
ANP [pg/ml]	94.2 ± 36.7	108.6 ± 46.4	134.5 ± 39.6*	131.2 ± 41.4*	164.8 ± 56.5#
BNP [pg/ml]	156.7 ± 52.1	169.3 ± 61.6	176.1 ± 70.8	181.2 ± 67.3	277.4 ± 79.7#

* - $p < 0.05$ vs CG and vs NG; # - $p < 0.01$ vs CG, vs NG, vs CR and vs EH

In conclusion: In hypertensive pts:
1. CH is accompanied by increased plasma levels of ANP and BNP, whereas CR and EH only by increased plasma level of ANP,
2. among all 4 patterns of LVG plasma levels of both ANP and BNP are the highest in group with CH,
3. plasma ANP level seems to be a good predictor of any change in LVG, while plasma level of BNP may be helpful in discrimination of CH.

P2340 Growth hormone prevents apoptosis in cardiomyocytes cultured in vitro

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Background: The use of growth hormone (GH) as a new therapy of heart failure has received considerable attention in recent years. However, the mechanisms by which GH influences cardiomyocyte cell function are largely unknown. In this paper we have tested the possibility that GH exerts a direct antiapoptotic effect on cardiomyocytes.
Methods and Results: Rat neonatal primary cultured cardiomyocytes (PC) were tested for GH receptor (GHR) expression. In HL-1 cardiomyocytes we performed GHR binding assays and western blot/immunoprecipitation studies to evidence expression and activation of GHR and classical downstream effectors induced by GH. Apoptosis was induced by serodeprivation or treatment with cytosine arabinoside (AraC) respectively. GH prevented apoptosis in serodeprivated (48h) PC, as assessed by DNA ladder electrophoresis, TUNEL assays (55.02±14.4% of control, $p<0.05$), and Hoechst dye staining (58.74±0.7% of control, $p=0.0102$). In HL-1 cells treated with GH+AraC, TUNEL revealed a decrease of apoptotic cells (24.64±0.35%) in comparison with those treated with AraC (44.87±3.25%; $p<0.001$). Anti-IGF-1 antibody treatment did not affect the antiapoptotic effect of the hormone. We used calcineurin phosphatase inhibitors cyclosporine (Cy) and FK-506 in order to dilucidate a possible role for this calcineurin phosphatase on GH effects on cardiomyocytes. By FACS analysis, HL-1 cells growing in normal medium displayed a 9.69% of apoptosis, AraC treatment increased apoptosis up to 21.09%, and GH reverted significantly this effect (13.9%). The combined treatment with AraC, GH and Cy/FK-506 increased newly the apoptosis rate to 21.46%. GH increased the percentage of cells in S/G2/M phase (52.83% vs 36.95% of AraC treated cells).
Conclusions: GH exerts an antiapoptotic effect on PC and HL-1 cells. Our data point to a direct effect of GH on cardiomyocytes not mediated by IGF-1, and this effect require the action of calcineurin phosphatase.

P2341 Procollagen peptides in essential hypertension and its relation to cardiac structure and functions before and after antihypertensive therapy

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Background and Aim: A significant increase in fibrillar collagen content type I and III has been observed in the cardiac ventricles of both animals and humans with arterial hypertension. The serum concentration of procollagen type I carboxy terminal peptide (PIP) and procollagen type III amino terminal peptide (PIIIP) has been proposed as a useful markers of collagen types I and III synthesis. Therefore, the present study was conducted to evaluate fibrogenic activity in patients with essential hypertension by measuring serum PIP and PIIIP as biochemical markers of tissue synthesis of collagen type I and III, and its relation to parameters of left ventricular (LV) structure and functions in those patients.
Methods: The study included 79 hypertensive patients and 50 normotensive control subjects. Mean age was 47 year. After clinical evaluation, echocardiography (M-mode, 2D, and pulsed Doppler) was done to evaluate LV anatomy and function. Serum PIP and PIIIP were measured by radioimmunoassy. Echocardiography and biochemical studies were repeated for the hypertensive patients after 6-month treatment with captopril.
Results: Serum PIP and PIIIP were significantly higher in patients than in control (258±57 and 3.73±2.2 mg/L versus 167±70 and 1.9±1.4mg/L respectively). In addition PIP and PIIIP were significantly higher in patients with LV hypertrophy (LVH) than in those with normal LV mass. Moreover, PIP level was directly correlated with LV mass index (LVMI). On the other hand, PIIIP level was inversely correlated with VE/VA ratio.
After treatment with captopril for six months, significant echocardiographic and biochemical improvements were observed. LVH regressed in 13 out of 68 patients (19%), LVMI was normalized in 17 out of 58 patients (29%), and diastolic dysfunction was normalized in 10 out of 44 patients (23%). Serum PIP and PIIIP were significantly reduced in hypertensive patients.
Conclusion: Serum level of PIP and PIIIP are significantly increased in hypertensives. Such increment was more evident and correlated with LVH patients. These changes improved significantly after treatment with captopril. So, biochemical monitoring of collagen fibril turnover might provide a potential non-invasive method of assessing myocardial fibrosis. Circulating procollagen derived peptides may reflect ongoing myocardial fibrosis in essential hypertension. The renin-angiotensin-aldosterone system may participate in the excessive synthesis of collagen type I and type III in hypertension.

P2342 Age-dependency of alpha-adducin polymorphism modulation of blood pressure

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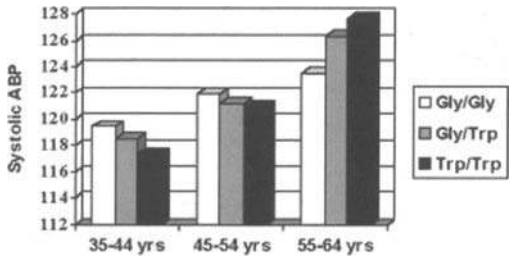
Considering that one large study from the HyperGEN Network suggested that alpha-adducin appears to be an important risk factor for hypertension particularly in older people, we decided to verify if our previous observation that a Gly-460-Trp polymorphism of the alpha-adducin gene is associated to blood pressure levels, in a sample of middle-age (50 to 65 years) general population, can be extended to younger individuals from the same population.
To evaluate if the relationship between a-adducin polymorphism and blood pressure may be influenced by the age of subjects.
We studied a randomly selected sample of the general population of an Italian town. Subjects were selected in the age range of 35 to 64. Blood pressure was measured by ambulatory monitoring (Spacelabs), with at least 60 measurements over a 24 hour period. In 414 Individuals phenotypic and genotypic data were available.
In the overall population sample, 24-hour ambulatory blood pressure (ABP) did not significantly differ among Gly-460-Trp genotypes. However, analysis of data after stratification by age (below vs. above median value, or according to tertiles of age) revealed a significant interaction (ANOVA, p=0.048) between classes of age and Gly-460-Trp genotypes on blood pressure, so that Trp460 is associated to blood pressure increase only in older subjects (> 55 years).



Our findings suggest that the association between the Trp460 allele and hypertension is influenced by age. It is hypothesizable that at older age, the pathogenetic effect of adducin mutation is more evident, possibly due to a reduced efficiency of compensatory mechanism(s). This observation underscores the necessity of taking into account an age-dependent effect when investigating genotype-phenotype interactions.

P2343 Neutral endopeptidase and angiotensin I converting enzyme insertion/deletion gene polymorphism in normotensive and hypertensive subjects

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Background: Neutral endopeptidase (NEP) hydrolizes angiotensins (Ang) I and II and generates angiotensin-(1-7). Angiotensin I converting enzyme (ACE) may influence Ang II levels and regulate the vasculature tone. In humans, the insertion/deletion (I/D) ACE gene polymorphism determines plasma ACE levels by 50%. The D allele is associated with increased ACE activity. In rats with a similar ACE polymorphism, high plasma ACE is inversely related to circulating and tissue NEP activity (Oliveri et al. Hypertension 2001; 38: 650-654).
Aims: To evaluate the relationship between ACE expression and NEP activity in normotensive and hypertensive human subjects.
Methods: Plasma ACE and NEP activities were determined in 37 normotensive subjects and in 40 untreated patients with essential hypertension. Both groups were homozygous DD ACE (high plasma ACE) or II (low plasma ACE). Normotensive subjects and hypertensive patients were similar in terms of age and gender distribution. Genotypes were determined by PCR.
Results: Plasma ACE activity was elevated by 70% ($p < 0.001$) in both DD ACE homozygous groups (normotensives and hypertensives) compared with both II ACE homozygous groups and it was 20% higher ($p < 0.01$) in both hypertensive groups (II and DD ACE homozygous) compared with both normotensive homozygous groups. No interaction between ACE genotypes with blood pressure status on ACE activity was observed. In the normotensive homozygous DD subjects, plasma NEP activity was 0.30 ± 0.02 U/mL and it was 64% higher ($p < 0.001$) in the normotensive homozygous II subjects, with a significant negative linear correlation between ACE and NEP activities ($r = -0.56$, $p < 0.01$). In the hypertensive homozygous DD patients, plasma NEP activity was 0.47 ± 0.03 U/mL without difference with the hypertensive homozygous II patients. Using ANOVA with 2 factors, a significant effect of the ACE genotypes ($F \approx 4.7$, $p < 0.02$) and also an interaction effect between the ACE genotypes and the blood pressure status (normotensive or hypertensive) on plasma NEP activity were observed ($F = 13$, $p < 0.002$).
Conclusions: These results are consistent with a modulatory effect of the ACE polymorphism on NEP activity in normotensive humans. High ACE expression is associated with low circulating NEP activity (and vice versa). This inverse relationship between ACE expression and NEP activity is not observed in hypertension. These observations could explain some pathogenic mechanisms in hypertension and some effects associated with the presence of the D ACE allele.
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P2344 Microvascular disease and abnormal endothelium-dependant arterial dilatation in essential hypertension

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Background: Arterial hypertension is a pivotal risk factor of endothelial dysfunction in conduit arteries representing a key trigger for atherosclerosis. A reduced flow reserve in resistance vessels is a hallmark of hypertensive microvascular disease. We hypothesized that microvascular abnormalities impair endothelium-dependent flow-mediated dilatation (FMD) in upstream conduit arteries in patients with essential hypertension.
Methods: Brachial artery endothelium-dependent FMD was measured in 43 hypertensive patients (HT) and 38 normotensive controls (NT) using high resolution ultrasound. Microvascular flow reserve (FR) in forearm resistance vessels was assessed by venous occlusion plethysmography.
Results: Brachial artery endothelium-dependent FMD was markedly impaired in HT (3.6±0.3%) as compared with NT (10.2±0.3%), whereas endothelium-independent dilatation was only slightly blunted. FMD was progressively impaired with increasing duration of hypertension. Microvascular flow reserve of forearm resistance vessels was significantly reduced in hypertensive patients (3.2 in HT versus 6.0 in NT). Brachial artery FMD was related to microvascular flow reserve in HT ($r=0.60$, $p<0.01$), but not in NT. Multiple stepwise regression analysis unmasked microvascular flow reserve as a strong independent variable determining the extent of brachial artery FMD ($r^2=0.45$, $p<0.01$). In hypertensive patients reversal of impairment in microvascular flow reserve improved brachial artery endothelium-dependent dilatation by more than 60%.
Conclusions: In essential hypertension microvascular disease may emerge as a novel, independent, and potentially reversible mechanism impairing flow mediated dilatation in conduit arteries. Microvascular abnormalities may thus become relevant to the pathogenesis and therapy of cardiovascular disease associated with arterial endothelial dysfunction.

P2345 The erythropoietin serum concentration in patients with essential arterial hypertension

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The role of erythropoietin (EPO) in the etiopathogenesis of essential hypertension (EH) is not univocally defined yet. EPO activates tissue RAAS, synthesis of endothelin and serotonin, exerts direct vasopressor effect and diminish influence of NO on the vascular smooth muscles. The aim of this study was to evaluate if endogenous EPO is a pathogenic factor in the EH.
Material and method: The study group consisted of 74 patients (pts) aged 17-79 years with EH, 43 women aged 20-79 years and 31 men aged 17-77 years. Control group consisted of 11 healthy volunteers, 4 women and 7 men, aged 20-71 years. The mild EH (by VI JNC standards) was noticed in 20 pts (MiEH), moderate EH in 34 pts (MdEH) and severe EH in 20 pts (SEH). The pts were also divided into 3 groups depending on the severity of organ damage (by WHO standards). 1st degree organ damage (dod) was observed in 13 pts (I group), 2nd dod in 49 pts (II group) and 3rd dod in 12 pts (III group). The blood samples for evaluation of EPO serum concentration was taken at baseline conditions and determined by the radioimmunological method using the Eritropoietine (Human) RIK no 6913 by Peninsula Laboratories INC. We also evaluated the echocardiographic parameters, renin plasma activity (ARO), plasma concentration of aldosterone, hematocrit, red blood cells count, creatinine concentration, creatinine clearance and 24-hours microalbuminuria.
Results: The baseline EPO was significantly higher in pts with SEH and 3rd dod than in control group (respectively 11.8±7.0 vs 6,9±4,3 ng/ml, $p<0.05$ and 12.5±8.9 vs 6,9±4,3 ng/ml, $p<0.05$). There was no statistically significant difference in baseline EPO between pts with MiEH, MdEH, 1st and 2nd dod and control group. In pts with MiEH EPO correlated positively with interventricular septum diameter ($r= 0.519$, $p<0.02$). In pts with MdEH and in pts with 2nd dod EPO correlated positively with ARO ($r= 0.424$, $p<0.01$ and $r= 0.288$, $p<0.04$). In pts with SEH EPO correlated positively with 24-hours microalbuminuria ($r= 0.574$, $p<0.01$). EPO correlated negatively with creatinine concentration ($r= -0.768$, $p<0.002$) and positively with creatinine clearance ($r= 0.769$, $p<0.002$) in pts with 1st dod. In pts with 2nd dod EPO correlated negatively with end-diastolic left ventricle diameter ($r= -0.291$, $p<0.04$).
Conclusions: We observed a significant elevation of EPO in pts with SEH and 3rd degree organ damage. EPO correlates also with different neurohumoral, biochemical and echocardiographic parameters. These findings suggest that EPO may contribute to development of the EH, what needs further investigations.

P2346 Abnormal ANP–type A-receptor – Dependent vasodilation in patients with essential hypertension: secondary to receptor downregulation?

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Endothelial-mediated vasodilation is impaired in patients with essential hypertension (eHYP) whereas the endothelium-independent relaxation mediated by the soluble guanylatzyclase (GC) pathway appears to be preserved. Little is known about the particulare GC pathway which is stimulated by atrial natriuretic peptide (ANP). Recently, a deletion mutation in the 5' flanking region of the ANP-receptor has been observed in japanese patients with eHYP (Circ Res.2000;86:841) which reduces the promoter activity by 33%. It was the purpose of our study to investigate the ANP-receptor-mediated vasodilation in eHYP. We included 45 patients with eHYP and 17 normotensive subjects (control group). Blood flow was measured in the forearm circulation by venous occlusion plethysmography during i.a. infucions of ANP (50-400 ng/min), acetylcholine (ACh; 15-30 μg/min) and sodium-nitroprussid (SNP, 1.6-3.2 μg/min). The table summarizes the maximal increases in blood flow (D% baseline, mean ± SD) (*$p<0.05$vs. eHYP).

	eHYP	control
ACh max.	51,2 ± 28,1%	76,8 ± 25,7%*
SNP max.	95,2 ± 30,1%	100,4 ± 26,1%
ANP max.	45,8 ± 24,9%	69,4 ± 25,2%*

In the study group as well as in additional patients with eHYP (n=200) no deletion mutation in the 5' flanking region of the ANP receptor could be detected using polymerase chain reaction. Plasma-levels of pro-ANP as an indicator of cumulative ANP-production were significantly elevated in patients with eHYP (n=90) as compared to controls (n=45) (3.31 ± 1.48 vs. 1.94 ± 1.12 pmol/ml; $p<0.01$).
Conclusion: The ANP-receptor mediated vasodilation is impaired in patients with eHYP as compared to normotensive controls. This impairment is not caused by a deletion mutation in the 5' flanking region of the ANP-receptor. The elevated plasma levels of pro-ANP suggest that downregulation of ANP-receptors may participate to this phenomenon.

P2347 Polymorphism in intron 23 of the endothelial nitric oxide synthase gene (NOS3) is not associated with hypertension

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Background: Impaired synthesis of NO due to mutations in the NOS3 gene is associated with hypertension. Several allelic variants of the NOS3 gene have been identified and evaluated for possible association with cardiovascular disease. The majority of NOS3 gene polymorphisms have been found in introns. The G11T polymorphism in intron 23 has not yet been widely investigated.
Aim: The purpose of our investigation was to determine the association of intron 23 polymorphism of the NOS3 gene with the incidence of hypertension.
Materials and methods: The study group consisted of 108 Caucasian patients (men-74, women-34) with arterial hypertension The patients ranged in age from 20 to 67 (median age 51). As a control group served 118 healthy individuals matched with sex and age. In our study we applied PCR-restriction fragments length polymorphism (PCR-RFLP) analysis with the use of restriction endonuclease NmuCI.
Results: The multitemperature single-stranded conformational polymorphism (MSSCP) analysis of the amplified fragment of the NOS3 gene showed three different banding patterns. Sequence analysis revealed three corresponding variants of G11T polymorphism in intron 23. Following PCR-RFLP analysis all the patients and the controls were divided into three groups: G/G, G/T and T/T, according to their genotype (table).

Group	Group size	Homozygotes T/T n (%)	Heterozygotes G/T n(%)	Homozygotes G/G n(%)	Allele frequencies (%) T—G
Patients	108	16(14,81)	52(48,15)	40(37,04)	39—61
Control	118	13(11.02)	55(46.61)	50(42,37)	34,3—65,7

Allelic Frequencies [patients vs control] $p = 0.31$ (X2 test) Genotype Distribution [patients vs control] $p = 0.32$ (U-test)

Conclusions: No major differences in the distribution of G11T polymorphism in the affected individuals and control groups were found (p=0.32). The present work shows that the G11T polymorphism of the NOS3 gene is not associated with hypertension.

ENDOTHELIAL FUNCTION

P2348 At the level of which vessels does flow-mediated dilation of the brachial artery correlate with coronary endothelial function?

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Background: Flow-mediated dilation (FMD) of the brachial artery has been widely used as an index of peripheral endothelial function. However, only a few studies have shown that the FMD of the brachial artery correlates with the endothelial function of coronary arteries. Furthermore, the vessel level at which the FMD of the brachial artery correlates with coronary endothelial function remains to be clarified. Therefore, we investigated whether the FMD of the brachial artery correlatesdwith coronary endothelial function at the level of conduit and/or resistance vessels. Methods: Thirty-nine patients (mean age: 62 yrs; 22 men and 17 women) with normal coronary arteries were enrolled for this study. Patients with myocardial infarction, heart failure, or other serious diseases were not included in the study. Changes in brachial artery diameter in response to hyperemic flow (FMD) were measured by high resolution ultrasound (10MHz) before coronary angiography. On coronary angiography, acetylcholine (Ach, 3 μg/min and 30 μg/min) was infused into the left coronary ostium over 2 min. The diameter of proximal and distal segments of the left anterior descending coronary artery was quantitatively measured and coronary blood flow (CBF) was calculated by quantitative angiography and Doppler flow velocity measurements. The changes in coronary artery diameter and CBF in response to Ach infusion were expressed as percent changes from baseline values. Results: FMD (4.8±0.6%) did not correlate with any changes in the coronary diameter induced by Ach at the proximal (Ach 3 μg/min: 0.8±1.0%, Ach 30 μg/min: -2.9±1.7%, both NS) nor at the distal segment (Ach 3 μg/min: -2.1±1.1%, Ach 30 μg/min: -4.8±2.2%, both NS). On the other hand, the FMD showed significant correlations with the increase in CBF induced by Ach at 3 μg/min (49±8%, r = 0.367, p = 0.0209) and 30 μg/min (86±16%, r = 0.357, p = 0.0271) dose levels. Conclusions: These results suggest that FMD of the brachial artery correlates with coronary endothelial function at the level of resistance vessels but not at that of conduit vessels. Interestingly, FMD of the brachial artery may be a useful index of coronary endothelial function at the level of resistance vessels.

P2349 Elevated serum C-reactive protein levels and early arterial changes in healthy children

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Background: Elevated serum concentration of C-reactive protein (CRP) predicts cardiovascular events in adults. As atherosclerosis begins in childhood, we undertook a study to determine whether changes in brachial artery reactivity and the thickness of the carotid intima-media complex, two markers of early atherosclerosis, are related to CRP levels in healthy children.

Methods and Results: Using high-resolution ultrasound, we measured brachial artery flow-mediated dilatation (FMD) and carotid artery intima-media thickness (IMT) in 79 children (age 10.5±1.1 years). As compared to the children with CRP levels under the detection limit (<0.1 mg/L, N=40, Group 1), the children with higher CRP (Group 2: 0.1 mg/L=< CRP < 0.7 mg/L, n=20; Group 3: CRP>0.7 mg/L, n=19) had lower brachial artery flow mediated dilatation (9.0±4.4 vs 7.8±3.3 vs 6.5±2.6%; univariate p=0.015 for trend) and greater carotid artery intima-media thickness (0.45±0.03 vs 0.46±0.04 vs 0.49±0.06 mm; univariate p=0.006 for trend). CRP level remained a statistically significant independent predictor for both brachial artery flow-mediated dilation and carotid artery intima-media thickness in multivariate analyses including age, sex, body size, serum lipids, blood pressure and intercellular adhesion molecule-1 concentration, as covariates (table).

	CRP-groups			p-value (trend)
	<0.1 mg/L	0.1-0.7 mg/L	>0.7 mg/L	
peak FMD, %	9.0 (4.4)	7.8 (3.3)	6.4 (2.6)	0.018
mean IMT, mm	0.41 (0.03)	0.42 (0.04)	0.44 (0.04)	0.012
max IMT, mm	0.45 (0.03)	0.46 (0.04)	0.49 (0.06)	0.014

The associations between CRP groups and the ultrasonic measures of arterial function and structure. Values are mean (SD). P-values from multivariate linear regression adjusted for age, sex, body mass index, mean blood pressure, total cholesterol, HDL-C, ICAM-1 and baseline arterial diameter (brachial or carotid).

Conclusions: These data suggest that CRP directly affects the arteries of healthy children by disturbing endothelial function and promoting intima-media thickening. The findings support the hypothesis that CRP has an important role in the pathogenesis of atherosclerosis.

P2350 Impact of physical activity on phosphorylation of endothelial nitric oxide synthase in patients with coronary artery disease

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Background: Regular physical exercise training (ET) is associated with a correction of endothelial dysfunction in patients (pts) with coronary artery disease (CAD). The molecular basis for this beneficial training effect, however is still unclear. Aim of this study was to assess the effects of ET on the expression and phosphorylation of endothelial nitric oxide synthase (ecNOS) in the endothelium of the left internal mammarial artery (LIMA) in pts with symptomatic CAD scheduled for elective bypass surgery (CABG).

Methods: Thirty-five pts with CAD were randomly assigned to either a training (T) or an inactive control (C) group. At study begin (B) and after 4 weeks (4 wks) endothelial-dependent vasodilation (eVD) in response to different dosages of acetylcholine (Ach) was assessed invasively with the help of a Doppler flow wire. The mRNA expression of eNOS was measured by real-time PCR in LIMA tissue not used for bypass grafting; the amount of phosphorylated ecNOS (serine 1177) (p-ecNOS) and phosphorylated protein kinase B (p-Akt) was quantified by Western Blot analysis.

Results: Acetylcholine-mediated (7.2 μg/min) average peak velocity (APV) (vs. 0.9% saline) increased significantly from 50±8 at B to 99±11% after 4 wks of ET (p<0.05 vs. C).The training group differed significantly from the C group with regard of ecNOS expression (6.1±1.2 vs. 3.1±0.6 rel. amounts; p<0.05 vs. C), p-ecNOS (serine 1177)(1.18±0.22 vs. 0.28±0.06 rel. amounts; p<0.01 vs. C), and p-Akt (1.31±.24 vs. 0.65±.1 rel. amounts; p<0.05 vs. C). The ecNOSmRNA/p-ecNOS ratio was significantly lower in T as compared to C (5.2±1.3 vs. 16.6±4.8; p<0.05).

There was a correlation between p-ecNOS and p-Akt (r=0.77, p<0.001) and between change in APV and p-ecNOS (r=0.56, p<0.002).

Conclusions: In patients with symptomatic CAD regular exercise training leads to a considerable improvement of agonist-mediated vasodilation of the LIMA. This beneficial training effect might on the cellular level be associated with a shear-stress induced/Akt-dependent increase in ecNOS phosphorylation.

P2351 Effect of pravastatin and chronic physical exercise on forearm blood flow in patients with coronary artery disease and average cholesterol levels

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Background: Improvement of forearm blood flow (FBF) by chronic exercise has been demonstrated in healthy volunteers, but studies in patients with coronary artery disease (CAD) are scarce. The purpose of this study was to investigate whether a 10-week (wk) treatment with pravastatin in patients with CAD and average cholesterol levels improves the endothelium-mediated vasodilatation of forearm arteries and whether this effect can be enhanced by physical exercise training.

Methods: 22 male patients with CAD and average cholesterol levels (<6,2 mmol/L) were randomised in three groups and investigated at baseline and after 10 wks. Group 1: 7 subjects received 40 mg pravastatin daily and did not change their lifestyle and recreational physical activity. Group 2 and 3: 15 subjects performed a structured endurance exercise program and were randomised in a double-blind trial to receive placebo (n=7) or 40 mg pravastatin (n=8). FBF changes were accessed with strain-gauge plethysmography.

Results: Sodium nitroprusside (SNP) and acetylcholine (Ach) caused a dose-dependent increase of the FBF that remained unchanged after pravastatin treatment and/or physical exercise training. In group 3, but not 1 and 2, the N-monomethyl-L-arginine (L-NMMA)-induced vasoconstriction was significantly greater at follow-up (0.72% (0.54-0.95) vs. 0.59% (0.38-0.70), p=0.03, baseline vs. follow-up).

Conclusion: Our observations indicate that a 10-wk therapy with 40 mg pravastatin combined with moderate endurance training improves the endothelial basal NO dilatator reserve in patients with CAD and average cholesterol levels. This is not achieved by either pravastatin therapy or exercise training alone. Concurrently, the stimulated NO release and the endothelium-independent vasodilatation remain unaltered.

P2352 Endothelial function is related to oxidized LDL and insulin resistance in healthy young men

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Background: Endothelial dysfunction is regarded as an early step in the development of atherosclerosis. Both LDL oxidation and insulin resistance play important roles in the pathogenesis of atherosclerosis. Furthermore, recent studies have suggested that there is a significant link between oxidized LDL (oxLDL) level and insulin resistance. In this study, we investigated the relationship between these factors and endothelial function in healthy young men.
Methods: Thirty-three men (aged 28.0±2.5 years), who had no history of atherosclerotic diseases, were enrolled in this study. Insulin sensitivity was estimated by homeostasis model assessment insulin resistance (HOMA-IR) and these subjects were divided into two subgroups according to HOMA-IR (insulin-resistant group with a HOMA-IR>=2.5, n=15; and insulin-sensitive group with a HOMA-IR<2.5, n=18). HOMA-beta-cell function was used to assess pancreatic insulin function. We evaluated endothelial function estimated by flow-mediated vasodilation during reactive hyperemia, using high-resolution ultrasound Doppler echocardiography. We also measured serum oxLDL level by a sandwich ELISA method.
Results: In the insulin-resistant group, body mass index, fasting glucose and insulin levels, HOMA-IR, and HOMA-beta-cell function were significantly higher and HDL-cholesterol level was significantly lower than those in the insulin-sensitive group ($p<0.01$, respectively). The serum oxLDL level was also significantly higher in the insulin-resistant group than in the insulin-sensitive group (133±42 vs. 105±34 U/L, $p<0.05$). Furthermore, the serum oxLDL level and HOMA-beta-cell function were significantly correlated with endothelium-dependent vasodilation (r=-0.568 and -0.521, $p<0.05$; respectively) in the insulin-resistant group. A stepwise multiple regression analysis in the insulin-resistant group showed that the serum oxLDL and fasting insulin levels were determinants of endothelium-dependent vasodilation (R^2=0.503). In contrast, the insulin-sensitive group showed no significant relationship between these parameters and endothelium-dependent vasodilation. There was no significant relationship between these parameters and endothelium-independent vasodilation induced by sublingual nitroglycerin in both groups.
Conclusion: These results suggest the possibility that LDL oxidation may be accelerated under the existence of insulin resistance and thus impair endothelial function in healthy young men.

P2353 Effects of vitamins C and E on thrombosis/fibrinolysis system in chronic smokers

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Background: Smoking is implicated in coronary artery disease and acute coronary thrombosis. Purpose of this study was to investigate the effect of antioxidant vitamins C and E on endothelial function and simultaneously on blood levels of plasminogen activator inhibitor (PAI-1) von Willebrand factor (vWF), tissue plasminogen activator (tPA) and factor VII (fVII) in smokers.
Methods: 43 healthy young smokers (23 males 20 females aged 36±2 years) were enrolled in this double blind placebo controlled study. Subjects were divided into 4 groups receiving vitamin C 2g/day (n=10) (group A), vitamin C 2g/day and vitamin E 400IU/day (n=12) (group B), vitamin C 2g/day and vitamin E 800IU/day (n=10) (group C) or placebo (n=11) (group D), for 4 weeks. Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to post reactive hyperemia blood flow. Endothelium independent % change flow (NTG%) was assessed after sublingual nitroglycerin administration. Plasma levels of PAI-1(ng/ml), vWf(%), tPA(IU/ML), and fVII(%) were determined by enzyme linked immunosorbent assay. All values are expressed as mean ± SEM.
Results: Blood pressure, heart rate, body weight, basal forearm blood flow and NTG% remained unchanged before and after treatment. FMD was significantly increased in group B (48.4±5.3 to 72.3±8.5%, $p<0.05$) and C (41.2±3.7 to 73.6±4.1%, $p<0.001$), while remained unaffected in groups A and D. Plasma levels of PAI-1 and vWF were decreased in group C (from 19.3±2.4 and 81.0±4.5 to 12.8±1.2 ng/ml and 68.5±3.1% respectively, $p<0.05$ for both), while remained unaffected in groups A, B, and D. Plasma levels of tPA and fVII did not change in none of the groups.
Conclusions: Combined administration of vitamin C 2g/day and vitamin E 800IU/day improves endothelial function and reduces blood levels of PAI-1 and vWF. These findings provide evidence that combined administration of vitamins C and E may affect thrombosis/fibrinolysis system in chronic smokers

P2354 Nitric oxide and prostaglandins mediate vascular effects of estrogen

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Estrogen has atheroprotective and vasodilative effects. The mechanisms of these effects are unknown. Nitric oxide (NO) and prostaglandins (PG) like prostacyclin (PGI2) are endogenous vasodilators and both are released from endothelial cells in response to similar stimuli. Thus they may be involved in the mentioned estrogen-effects. This study examined, whether inhibition of NO-synthesis by L-NAME or inhibition of PG-synthesis by indometacin (INDO) modulates the vascular effects of 17beta-estradiol (17b-E) in vivo.
Methods: The effects of 200 ng/kg 17b-E were compared with NaCl-controls in open-chest female rats without and after pretreatment with 100 mg/kg L-NAME or 5 mg/kg INDO or after pretreatment with L-NAME and INDO. To quantify myocardial contractility isovolumic measurements (i. dP/dtmax) were performed. Additionally plasma levels of 6-keto PGF1a,the stabile metabolite of PGI2, were determined before and after infusion of 17b-E.
Results: 17b-E increases cardiac output and ejection fraction due to a reduction of the afterload. This effect is significantly reduced by INDO and completely abolished by L-NAME or by combined pretreatment. 17b-E has no inotropic effect. Infusion of 17b-E causes an increase of the 6-keto PGF1a plasma level from 2.9±0.5 ng/ml to 3.4±0.5 ng/ml.

	CO	EF	TPR	i. dP/dtmax
17b-E	167±10¶	127±3¶	71±3¶	97±4
NaCl	108±5	98±3	96±4	102±3
L-NAME + 17b-E	109±2	104±3	93±2	101±1
L-NAME + NaCl	113±2	106±5	92±3	98±2
INDO + 17b-E	135±5¶	114±5*	81±2*	98±2
INDO + NaCl	100±2	99±1	100±2	101±2
L-NAME + INDO + 17b-E	116±3	109±3	92±3	99±3
L-NAME + INDO + NaCl	115±4	111±4	89±3	96±3

Mean ± SEM in % of preinfusion values before 17b-E- or NaCl-infusion; *=p<0.01, ¶=p<0.001.

Conclusions: The estrogen-induced vasodilation is caused by NO-release since this effect is completely prevented by L-NAME. A part of the effect is mediated by PG. The combined pretreatment also completely prevents the vasodilation by 17b-E. Thus it seems possible that NO, which is released by 17b-E, itself releases PG.

P2355 Relationship between endothelial nitric oxide synthase gene polymorphisms and coronary vascular function among subjects with CHD

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Background: Nitric oxide has an important role in endothelial function and integrity. There is evidence for a relationship between endothelial nitric oxide synthase (eNOS) gene polymorphisms and vascular function, but results are inconsistent.
Methods: This study was performed among 316 subjects enrolled in the ENCORE I study (mean age 58+10, 81% male). Inclusion criteria for the ENCORE I study were presence of CHD and pathological response to acetylcholine. With QCA, mean segment vessel diameter was determined at baseline and in response to acetylcholine (0.36, 3.6 and 18 µg/ml), adenosin (1.2 mg/ml) and nitroglycerin (200 µg). The eNOS gene polymorphism T-786C of the promotor region and the polymorphism G894T (Glu298Asp) in exon 7 were determined using PCR. The association of polymorphisms with QCA was tested with ANCOVA, adjusting for assessed segments, age and sex.
Results: CC homozygosity for T-786C was associated with a reduced baseline mean segment diameter (1.71 vs. 1.88 mm, p=0.02), and TT (G894T) carriers also had a non-significant reduction in segment diameter (1.79 vs. 1.86, p=0.40). Response to acetylcholine was similar among homozygotes compared to the remainder (CC vs TT/TC: mean response -23% vs. -20%, p=0.43; TT vs GG/GT: -20% vs. -20%, p=0.95; homozygosity for both variants, -25% vs -20%, p=0.44). Patients with the CC (T-786C) genotype tended to have an elevated response to nitroglycerin (21% vs 17%, p=0.16) and adenosin (18% vs 14%, p=0.18). In subjects who carried both the CC and TT variant response to nitroglycerin was significantly elevated (28% vs. 19%, p=0.04).
Conclusion: Our findings are compatible with a reduced basal endothelial NO production among CC and TT homozygotes of the T-786C and G786T eNOS gene polymorphisms supporting the hypothesis that these gene variants may be functional.

P2356 Cardiovascular events in patients with normal coronary angiogram but endothelial dysfunction of epicardial artery

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Little information is available to prove the relation between impaired endothelial-dependent vasomotion and cardiovascular events in long-term. We aimed to determine prospectively the prognostic impact of abnormal endothelial-dependent vasoreactivity of epicardial coronary artery in response to cold pressor testing (CPT) in patients with risk factors for atherosclerosis but normal coronary angiogram.

Method: In 141 patients with normal coronary angiogram, endothelial-dependent vasoreactivity in response to CPT and dilation of epicardial artery to intracoronary application of nitroglycerin was assessed quantitatively (%change of luminal area: delta LA%). Cardiovascular events (cardiovascular death, unstable angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary bypass grafting, ischemic stroke, or peripheral revascularisation) were assessed as clinical outcome parameters over a median follow-up period of 45±7 months. Patients were assigned on the basis of their endothelial-dependent vascular responses to CPT into 3 groups: group 1 (delta LA:>0%; n=25), patients with normal endothelial-dependent vasodilation; group 2 (delta LA:0% to -15%; n=51), patients with moderate endothelial-dependent vasoconstriction; and group 3 (delta LA:<-15%; n=65), patients with severe endothelial-dependent vasoconstriction.

Results: None of the patients from group 1 had cardiac events. However, in group 2 six (11%) and group 3 thirty-two (49%) cardiovascular events occurred ($p<0.05$ versus group 1, respectively). Patients suffering from cardiovascular events during the follow-up (group 2 and 3) had significantly increased flow-mediated vasoconstriction to CPT as compared to group 1 (mean delta LA:-14±5% versus 15±13%;$p<0.03$), but normal endothelial-independent vascular responses to intracoronary apllication of nitroglycerin (P=NS). Impaired endothelial-dependent epicardial coronary reactivity in group 2 and 3 was associated with a significantly higher incidence of cardiovascular events by Kaplan-Meier analysis ($P<0.0001$).

Conclusion: Abnormal endothelial-dependent vasoreactivity of epicardial coronary artery is associated with increased cardiovascular events. These findings suggest that assessment of endothelial-dependent vasomotion of epicardial coronary artery in response to cold pressor testing may provide valuable diagnostic and prognostic information during routine coronary angiography.

P2357 Increased serum soluble heat shock protein 60 levels are associated with endothelial dysfunction in patients with coronary artery disease

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Background: Recent clinical and experimental studies have suggested a significant role of soluble heat shock protein 60 (sHSP60) in inflammation and immune activation underlying atherosclerotic disease. Endothelial dysfunction is also considered to be one of the earliest events in the atherogenic process. The aim of our study was to investigate whether an association exists between sHSP60 and endothelial function in patients with coronary artery disease (CAD).

Methods: We examined 55 men (mean age 68±9yrs) with angiographically documented CAD (34 pts had multivessel disease). In all patients endothelial function was assessed by measuring flow mediated dilatation (FMD) of the brachial artery using high resolution ultrasound and standard methods. sHSP60 was measured by use of a sandwich enzyme-linked immunosorbent assay (ELISA)

Results: FMD of the brachial artery in these patients was 2.87±2.05%. The median [interquartile range] of sHSP60 was 458[131-935.6]ng/ml. sHSP60 had a skewed distribution and was logarithmically transformed before analysis. Univariate analysis showed a significant inverse relation between FMD and sHSP60 levels (beta=-1.90, $R^2=0.39$, $P<0.005$) indicating that endothelial dysfunction was more prominent in patients with higher sHSP60 concentrations. Multivariate analysis revealed that this association remained significant even after adjustment for other variables such as age, smoking, history of diabetes and hypertension, and lipid levels (P=0.002).

Conclusions: Our results showed that high levels of sHSP60 are associated with impaired endothelial function in patients with CAD. These findings indicate that this protein may play an important pathogenic role in the development of atherosclerotic heart disease.

P2358 Endothelial nitric oxide synthase and angiotensin-converting enzyme gene polymorphisms and the indices of arterial structure and function

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Endothelial nitric oxide exerts important effects on the regulation of vascular tone and structure. Genes regulating nitric oxide release have been suggested as a candidate genes involved in the development of hypertension.The ACE gene polymorphism is regarded to be a distinct heritable cardiovascular risk factor.

The aim of this study was to assess the contribution of two polymorphisms of the endothelial nitric oxide synthase (eNOS) gene and ACE gene polymorphism to aortic stiffness and carotid intima-media thickness in normotensive and hypertensive patients.

Material and methods: We studied 81 untreated hypertensive patients and 56 normotensive subjects. ABPM (SpaceLabs 90207) was performed in all subjects. Pulse wave velocity (PWV) between the carotid and femoral arteries was used as an index of arterial compliance (Complior device) and carotid intima media thickness (IMT) measured by carotid ultrasound was used as an index of arterial structure. The two eNOS gene polymorphisms: a biallelic variable number of tandem repeats (VNRT) in intron 4 and an exon 7 variant (G894T) that leads to Glu298Asp change were genotyped by PCR. The insertion/deletion(I/D) polymorphism for ACE gene was detected using polymerase chain reaction technigue.

Results: The distribution of genotypes and allele prevalence of eNOS polymorphisms among hypertensive and normotensive subjects were similar.The ACE genotype freguency was at Hardy-Weinberg eguilibrium. There was no association between Glu28Asp and VNRT polymorphism with blood pressure. No evidence of genetic influence was found in respect to pulse wave velocity. However, we observed that patients carrying T allele of Glu298Asp polymorphism had higher IMT (GG - 0.71 ± 0.1 mm, TG 0.95 ± 0.06 mm, TT - 1.32 ± 0.1 mm, $p<0.03$).No influence of ACE polymorphism on the indices of arterial structure and function was not observed.

Conclusion: These results indicate that the Glu28Asp polymorphism of eNOS identifies patients with increased carotid intima media thickness.

P2359 Effect of angiotensin-converting enzyme inhibition and AT1-receptor antagonism on myocardial perfusion in patients with endothelial dysfunction

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Background: It has been shown that statins improve myocardial perfusion in patients with hypercholesterolemia, possibly by improving endothelial function. Both ACE-inhibitors and AT1-receptor-antagonists have been shown to improve impaired endothelium-mediated vasodilation, i.e. long term quinapril therapy improved coronary endothelial function in the TREND trial. It is unclear, however, whether this beneficial effect on endothelial function is translated into improved myocardial perfusion or coronary flow reserve in normocholesterolemic patients with endothelial dysfunction.

Methods and Results: To test this hypothesis, we randomized 18 normocholesterolemic patients with typical anginal chest pain without significant coronary artery stenoses and with abnormal endothelial function (epicardial vasoconstriction and impaired coronary flow response to intracoronary acetylcholine infusion) to a 3 month therapy with quinapril (40 mg/d; n=11) or losartan (100mg/d; n=7). Myocardial perfusion at rest and after adenosin (140 µg/kg/min i.v.) was assessed using positron emission tomography (PET; C11-acetate) before and after therapy. Regional coronary flow reserve (CFR) was calculated from maximal myocardial blood flow after adenosin and blood flow under resting conditions. In patients treated with quinapril myocardial perfusion at rest was unchanged after therapy. However, maximal perfusion after adenosin was improved in every patient with 3 month quinapril, leading to restoration of regional CFR (from: 2.3 ± 0.3 to 3.5 ± 0.5; $p<0.05$). In patients treated with losartan, however, myocardial perfusion at rest, after adenosine and CFR was not significantly changed after 3 month therapy.

Conclusion: Longterm-ACE-inhibition restores regional coronary flow reserve in patients with endothelial dysfunction in the coronary circulation. Conceivably, this beneficial effect of long-term ACE-inhibition may be related to the documented improvement of quinapril on coronary endothelial function in this patient population.

P2360 Characterization of L-selectin-dependent adhesion to human microvascular cardiac endothelial cells

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L-selectin ligands are heavily glycosolated proteins and characterized by o-linked sugars and the MECA79 epitope. L-selectin is constitutively expressed on nearly all leukocytes and plays an important role for recruitment of leukocytes into inflamed tissues. Functional data suggest that - apart from the MECA79 epitope - additional adhesion receptors for L-selectin are of importance. Aim of the present study was to characterize endothelial cells with regard to sugar moieties which mediate L-selectin-dependent adhesion of leukocytes to endothelial cells. Endothelial cells from the microvasculature of human hearts (MEC) were isolated from explanted human hearts by enzymatic treatment of the heart tissue and further purified with ulex europaeus-linked paramagnetic beads. Upon confluence MEC were stimulated with TNF alpha (4 hours, 500 U/ml). L-selectin-dependent adhesion was quantified at different shear stress levels (0.6-2.6 dyn/cm^2) in a flow chamber using NALM6 cells stably transfected with L-selectin (NALM6-L). In addition, leukocyte rolling velocities (V) were measured at 1.5 dyn/cm^2. NALM6-L adhered shear stress-dependent to TNF-stimulated MEC but not to unstimulated MEC. V were reduced from 2.3-5 mm/s (median 3.7) on unstimulated MEC to 1.8-4 mm/s (median 2.7) on TNF-stimulated MECs. Inactivation of o-linked sugar moieties on MECs with O-sialoglycoprotein peptidase had no influence on adhesion and V. Inhibition of N-glycosilation with tunicamycin (10 μg/ml) inhibited adhesion and increased V of NALM6-L on MECs. MECA79 was neither expressed on unstimulated nor on TNF-stimulated MECs as judged from flow cytometry. The results suggest that - in contrast to lymphatic endothelium - N-glycosolation of L-selectin ligands are of importance on vascular endothelial cells while O-linked sugar moieties and the MECA79 epitope are functionally not relevant.

P2361 Decrease of CRP serum levels determines the extent of Statin induced improvement in endothelial dysfunction

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Statin therapy is associated with improved endothelial vasodilator function. Recent studies suggest that the beneficial effects of statins on atherosclerosis disease progression are most prominent in patients with elevated inflammatory markers. Since endothelial dysfunction importantly contributes to atherosclerotic disease progression, we investigated whether the antiinflammtory effects (as measured by CRP serum levels) of statins correlate with improved endothelial function in patients with CAD. Systemic vasoreactivity was assessed in 20 consecutive patients with documented coronary artery disease measuring endothelium-dependent (acetylcholine, ACH, 10-50μg/min) and endothelium-independent (sodium-nitroprusside, SNP, 2-8μg/min) forearm blood flow (FBF) responses by venous occlusion plethysmography, before and after initiation of a therapy with 20 mg atorvastatin daily.

Results: Atorvastatin treatment resulted in a significant and profound reduction of LDL-cholesterol levels by 48.1 ± 3.6% ($p<0.05$) and CRP serum levels from 1.8 ± 0.6 to 0.6 ± 0.4 mg/dl ($p<0.05$). ACH induced FBF responses increased significantly after 4 weeks of atorvastatin therapy (+414.9 ± 179.7%). There was a close significant inverse correlation of increase in FBF responses to ACH with reduced CRP levels ($r=-0.6; p<0.05$), but not with the decrease of LDL-cholesterol levels. A decrease in CRP serum levels was the most important independent predictor of improved endothelial vasodilator function.

Conclusion: Atorvastatin induced improvement in endothelial dysfunction is closely associated with its antiinflammatory effects as measured by CRP, but independent of cholesterol lowering in patients with CAD. These results further support the importance of pleiotropic mechanisms to mediate vasciloprotective effects of statins.

P2362 Obesity and waist/hip ratio predict endothelium-dependent coronary vasoreactivity in postmenopausal women

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Background: Obesity and body fat distribution have both been shown to be predictors of coronary heart disease (CHD). There is also an association between obesity and body fat distribution with impaired endothelium-dependent vasodilation in the peripheral as well as the coronary circulation.

Methods: We sought to noninvasively determine both endothelium-dependent and -independent measures of coronary vasoreactivity using dynamic N-13 ammonia positron emission tomography (PET). Myocardial blood flow (MBF) and myocardial flow reserve (MFR) were measured in 17 postmenopausal women (60±6 yrs) at risk for coronary heart disease. Mean body mass index (BMI) was 29.3±4.3 kg/m^2; mean waist-hip ratio (W/H) was 0.85±0.05. All subjects had elevated total and LDL cholesterol levels, as well as at least one additional CHD risk factor, and were not using hormone replacement therapy. All had negative dobutamine echocardiograms. MBF was measured using a three-compartment model at rest, in response to sympathetic stimulation with the cold-pressor-test (CPT), and to intravenous adenosine infusion, in order to determine baseline, endothelium-dependent, and endothelium-independent measurements, respectively. MFR was measured as the ratio between MBF during adenosine to MBF at rest. MBF and MBF normalized to the pressure rate product (PRP) were analyzed.

Results: There was a significant inverse correlation between BMI and normalized CPT MBF ($R= -0.605$, $p=0.010$). We also noted a significant inverse correlation between W/H ratio and CPT MBF ($R= -0.574$, $p=0.016$). There was a strong trend towards an inverse correlation between W/H and normalized CPT MBF ($R= -0.467$, $p=0.059$). No relationship was found between W/H or BMI and endothelium-independent flow, as assessed by maximal MBF after adenosine, or between W/H or BMI and MFR.

Conclusions: Both degree of obesity and visceral adiposity in postmenopausal women predict impaired endothelium-dependent coronary vasomotor responsiveness, as measured noninvasively by CPT PET.

P2363 Endothelial function in patients with severe coronary artery disease treated with enhanced external counterpulsation therapy (ECPT)

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Background: Enhanced external counterpulsation therapy (ECPT) reduces angina and improves exercise tolerance in patients with coronary artery disease (CAD). Vascular endothelium plays a key role in circulatory homeostasis. In CAD patients the vascular endothelium is usually impaired, and it has been suggested that modification or reversal of endothelial dysfunction may be of significant therapeutic benefit in the treatment of CAD patients. However, the impact of short-term ECPT on flow-mediated dilation (FMD) in CAD patients has not yet been assessed.

Methods: We prospectively assessed endothelial function in CAD patients with severe stable angina pectoris [Canadian Cardiovascular Society Classification (CCSC) III or IV] unsuitable for coronary revascularization (either coronary artery bypass grafting operation or percutaneous coronary intervention), before and after ECPT. Endothelium-dependent brachial artery FMD and endothelium-independent nitroglycerin-mediated vasodilation (NTG) were assessed using high resolution (16 MHz) linear array ultrasound in 10 consecutive severe CAD patients (mean age 66±11 years, mean left ventricular ejection fraction 47±9%, mean body mass index 28±3 kg/m^2), in an ongoing, single center trial. All patients completed a full 35-hour treatment course.

Results: See table.

	%FMD	%NTG	No. SL NTG/day	CCSC
Before ECPT	3.5±5.0	7.5±2.4	4.7±2.9	3.3±0.4
Post ECPT	8.2±3.5	8.7±4.6	0.4±0.5	2.0±0.4
p-value	0.03	0.55	<0.01	<0.01

Values are expressed as mean±SD; %FMD, %NTG = % change from baseline in brachial artery diameter caused by FMD and NTG, respectively; SL NTG=number of sublingual nitrates pills per day; CCSC = Canadian Cardiovascular Society Classification.

Conclusion: CAD patients with severe anginal syndrome unsuitable for coronary revascularization suffer from impaired brachial artery endothelium-dependent, flow-mediated vasodilation, suggesting the presence of endothelial dysfunction. ECPT significantly improves vascular endothelial function, thereby suggesting that such a mechanism could improve anginal and heart failure symptoms.

P2364 Effects of exercise on the expression of NAD(P)H-oxidase and angiotensin-II receptors in the LIMA of patients with coronary artery disease

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Introduction: In patients (pts) with coronary artery disease (CAD) physical activity (PA) has the potential to improve endothelial dysfunction. Several studies demonstrated that free oxygen radicals reduced the bioavailability of nitric oxide, a potent regulator of endothelial function. The aim of this study was to analyze the impact of PA on the expression of NAD(P)H-oxidase and angiotensin-II receptors (Ang-IIR) in the left mammarial artery (LIMA) of pts with CAD.
Methods: Thirty-five pts with the indication for a bypass surgery were randomized into either a training (T) or inactive control group (C). After 4-weeks the acetylcholine (ACH) mediated vasodilation of LIMA-rings in an organ bath and the expression of NAD(P)H-oxidase (subunit gp91phox and p22phox) and Ang-IIR (subtype 1 and 2) by real time PCR were analyzed.
Results: To induce a 50% relaxation (ED50) of phenylephrine-preconstricted LIMA-rings a significant lower concentration of ACH was necessary in T (7.6±0.3 [-log molar ACH]) as compared to C (6.9±0.2 [-log molar ACH]; $p<0.05$). The molecular analysis revealed that the expression of gp91phox (T: 0.36±0.12 vs. C: 2.06±0.62; $p<0.05$) and of p22phox (T: 1.67±0.47 vs. C: 4.79±1.5; $p<0.05$) was significantly reduced in T as compared to C. Additionally under the influence of PA a significant reduction of Ang-IIR subtype-1 (T: 3.6±0.79 vs. C: 16.6±5.7; $p<0.05$) and a significant increase of Ang-IIR subtype-2 (T: 2.6±0.61 vs. C: 0.48±0.21; $p<0.001$) was detected.
Conclusion: The results of this study demonstrate that also in the LIMA PA leads to an improvement of endothelial mediated vasodilation. At the molecular level this improvement may be due to a reduced expression of ANG-IIR subtype-1 and NAD(P)H-oxidase.

P2365 Chemokines (MCP-1, MIP-1a and RANTES) activation in acute myocardial infarction

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C-C chemokines are major factors in the recruitment and activation of monocytes and neutrophiles from the circulation into inflammed tissue and may play a role in acute myocardial infarction (AMI). The aim of this study was to assess the kinetics of three chemokines: Monocyte Chemoattractant Protein-1 (MCP-1), Macrophage Inflammatory Protein-1a (MIP-1a) and Regulated on Activation Normal T cell Expressed and Secreted (RANTES) serum level in patients with AMI.
Material and method: The study group consisted of 20 patients (pts) aged 43-79 (mean age 63,3) with AMI, 8 women and 12 men. Control group consisted of 10 healthy, sex- and age-matched volunteers. The blood samples for evaluation of MCP-1, MIP-1a and RANTES serum level was taken at the admission to the hospital, 3 hours (h) after thrombolytic therapy was started, then 24, 48 and 72 h and 7 days after admission. All chemokines serum level was determined by ELISA. In all pts we also measured serially during the first week of hospitalization serum creatinine kinase (CPK), serum creatinine kinase MB isoenzyme (CKMB), troponine I (TnI), white blood cells count and on the 3rd day after admission the echocardiography was made.
Results: The baseline MCP-1 and RANTES serum level was significantly higher in pts with AMI than in control group (MCP-1 836,1 vs 128,8 pg/ml $p<0,001$; RANTES 78,6 vs 31,3 pg/ml $p<0,01$). In pts with AMI there was a significant increase MCP-1, MIP-1a and RANTES serum level 3 h after thrombolytic therapy (MCP-1 1400,3 vs 836,1 pg/ml $p<0,01$; MIP-1a 70,4 vs 15,1 pg/ml $p<0,005$; RANTES 156,3 vs 78,6 pg/ml $p<0,01$). The MCP-1 and MIP-1a peak levels were 24 h after admission (MCP-1 1458,7 vs 836,1 pg/ml $p<0,01$; MIP-1a 91,9 vs 15,2 pg/ml $p<0,001$) and RANTES peak serum level was 3 h after thrombolytic therapy (156,3 vs 78,6 pg/ml $p<0,01$). MCP-1, MIP-1a and RANTES serum level was higher in pts with AMI also untill 7 days after admission. On the 3rd day the echocardiography examination was made and ejection fraction (EF) correlated negatively with chemokines, especially with MCP-1 ($r=-0.66$, $p<0.05$). Conclusions. In this preliminary report we detected a significant elevation of MCP-1, MIP-1a and RANTES serum level in pts with AMI during the 7 days of observation. The chemokines serum level correlated with cardiac marker proteins and statistically significant negative correlation with ejection fraction was found. These findings suggest that enhanced immune processes in AMI are connected with disease-related endothelial damage and may contribute to its pathophysiology, what needs further investigations.

P2366 -786C/T Gene polymorphism of endothelial nitric oxide synthase as a risk factor for coronary heart disease

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Background: Coronary heart disease (CHD), ultimately leading to myocardial infarction or heart failure, is based on the development of atherosclerosis in one or more coronary arteries. Shear stress-dependent endothelial nitric oxide release not only contributes to local blood pressure control but also helps to retard atherosclerosis. Functionally relevant polymorphisms in the endothelial nitric oxide synthase (NOS-3) gene may thus contribute to the development of CHD.
Methods: To verify this hypothesis, genomic DNA was isolated from the blood of patients undergoing coronary angiography and genotyped for the -786C/T polymorphism of the NOS-3 gene by restriction fragment length polymorphism analysis. In addition, shear stress-induced NOS-3 expression in endothelial cells isolated from genotyped umbilical cords was determined at the mRNA and protein level.
Results: Shear stress-induced NOS-3 expression was detected in -786T/T and -786C/T but not -786C/C genotype endothelial cells. Moreover, in patients below 65 years of age with angiographically proven CHD, the -786C/C genotype was significantly more frequent (19%) than in patients without CHD (2.5%, $P<0.0001$). The primary CHD risk factor profile, on the other hand, was the same in all patients irrespective of the genotype.
Conclusions: The -786C/T polymorphism of the NOS-3 gene, namely the -786C/C genotype, may thus constitute an independent risk factor for the development of CHD, presumably due to an alteration of the shear stress-responsiveness of the C-type promoter.

P2367 Determinants of plasma homocysteine levels in coronary patients

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Background: Hyperhomocysteinemia is an emerging coronary risk factor. This study aimed to evaluate the major plasma determinants of plasma homocysteine in patients with coronary artery disease.
Methods: We studied 636 patients with angiographically documented coronary disease (CAD). Fasting (>12hours) total plasma homocysteine (tHcy) taken at time of angiography were measured by fluorescence polarization immunoassay (IMx, Abbott Laboratories), methylenetetrahydrofolate (MTHFR, C677T) gene status was determined by polymerase chain reaction-restriction fragment length polymorphism and folate and vitamin B-12 by dualcount solid phase no boil assay (Diagnostic Products Corporation).
Results: Mean tHcy of the CAD group is 10.2±1.4mmol/l, being lowest in patients with CC genotype and normal folate levels (9.6mmol/l), and highest in patients with TT or CT genotype and folate deficiency (13.1mmol/l). The frequency of CC, CT and TT MTHFR polymorphisms were 59%, 35.8% and 5.2% respectively. On multivariate linear regression, age, plasma creatinine, folate, vitamin B-12 and TT genotype were independently correlated with tHcy levels (model $R=0.64$; F value=62.6; $p<0.001$), with significant interaction between plasma folate and TT genotype.

Clinical Paremeter of CAD Patients

	Standardized Coefficients	p-Value
Age	0.13	<0.001
Plasma creatinine	0.37	<0.001
Plasma vitamin B-12	-0.38	<0.001
Plasma folate	-0.14	<0.001
TT genotype	0.83	<0.001
TT plus plasma folate	-0.66	0.001

Conclusion: Plasma folate and vitamin B-12 levels, renal function and MTHFR genotype are major determinants of tHcy; folate profile is particularly determinative in TT genotyp

P2368 Different significance of soluble VCAM-1 and ICAM-1 in patients with acute versus chronic coronary syndromes

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Background: Soluble vascular cell adhesion molecule (sVCAM-1) and intercellular adhesion molecule (sICAM-1) are likely to reflect surface levels of molecules mediating adhesion and transmigration of leukocytes to the vascular endothelial wall and promoting plaque growth and instability.
Aim: To assess whether sVCAM-1 and sICAM-1 are increased in patients (pts) with coronary artery disease and whether they are differently regulated in acute versus chronic coronary syndromes.
Methods: We obtained plasma samples from 76 pts. 27 pts had acute coronary syndromes (ACS; 14 unstable angina, Braunwald IIIb, 3 nonSTEMI and 10 STEMI). Diagnosis of myocardial infarction was based on clinical data, modifications of the ECG and of the markers of myocardial damage (troponin, myoglobin). 37 pts had chronic coronary syndromes (CCS); in 12 of them, with positive exercise stress test, plasma samples were also collected before and after an exercise stress test (ST pre and ST post). 12 were control non-coronary patients. Quantitative determination of sVCAM-1 and sICAM-1 was performed by ELISA. C-reactive protein (CRP) and von Willebrandt factor (vWF) were also assessed by immunonephelometric and immunoenzimatic methods, respectively.
Results: See table.

	No. pts	sVCAM-1 (ng/ml)	sICAM-1 (ng/ml)	VWF (U/dL)	CRP (mg/dL)
ACS	27	749 (563-831)(**) (°°)	311 (251-370)(**)	196 (152-228)(**)	1.02 (0.56-1.71)(*)(°)
CCS	37	389(360-500)	309(260-352)(**)	127(94-160)(*)	0.41(0.25-0.50)
ST pre	12	461 (354-555)	352(340-370)	139(87-150)	0.46(0.25-0.50)
ST post	12	523(427-681)	416(378-447) (¶¶)	145(90-154)	0.44(0.26-0.55)
Controls	12	415(381-452)	204(188-230)	98(85-112)	0.31(0.05-0.52)

For abbreviations see text. Values are expressed as median (interquartile range). (**): p<.01 vs controls. (*): p<.05 vs controls. (°°): p<.01 vs CCS. (°): p<.05 vs CCS. (¶¶): p<.01 vs ST pre.

Conclusions: 1)sICAM-1 was significantly increased both in ACS and in CCS compared to controls, as well as after stress induced ischemia. 2)sVCAM-1 was significantly increased in ACS compared to CCS and controls; no significant difference was observed between CCS and controls. While sICAM-1 may be considered a marker of chronic coronary disease, sVCAM-1 appears more related to disease instability.

P2369 Association between multiple cardiovascular risk factors and endothelium dysfunction with myocardial infarction before 40 years of age

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Cardiovascular disease (CD) is a multifactorial disorder. Between 2 –6% of myocardial infarctions occur in subjects younger than 40. Althought traditional risk factors, such as hypertension, dyslipidemia, overweight, are significantly associated with CD, a significant number of coronary events remain of unknown ethiology. There is evidence that the younger the age of occurrence the greater the impact that genetic factors play on CD incidence. CD in youth is related to monovasal or to widespread atherosclerotic lesions, none of which of significant severity in its own right. Also, impairment of endothelial function is thought to trigger acute coronary events. We performed a case-control study for a through assessment of the risk profile in young coronary patients and we aimed at correlating it with changes in their endothelium-dependent vasodilatation and with the presence of atherosclerotic lesions, both in coronary and in carotid arteries.
Methods: 48 subjects with previous myocardial infarction and younger than 41 years of age, from the same geographical area. Patients were matched 1:1 with random sample controls, according to age and sex. We evaluated serum concentrations of total, HDL, and LDL cholesterol, triglycerides, fibrinogen, homocysteine, folic acid, vitamin B12, vitamin E, antioxidant capacity, uric acid, and Helicobacter pylori, and we searched for C667T and T1298C genetic mutations for MTHFR and CBS genes. Post-ischemic vasodilatation of the brachial artery was studied as index of endothelial function and all patient underwent an echo-color-doppler study of common and internal carotid arteries for the measurement of intima-media thickness (IMT).
Results and Discussion: Education, BMI, smoking habits, familiarity, apoE4 genotype, MTHFR genotype, dyslipidemia, HDL, sistolic and diastolic pressure, fibrinogen, vitamin E level, antioxidant capacity, vasodilatation (evaluated both as actual dilation and percent increase over controls), and IMT were significantly different between cases and controls. Through a statistical multivariate comparison among block variables, we noted that smoking, apoE genotype, dyslipidemia, plasma fibrinogen and vitamin E concentrations, and IMT are important predictors, exhibiting an accuracy of 91%. Such premature occurrence of acute coronary event warrants the screening of siblings for the assessment of their risk profile.

P2370 Modulation of endothelial function as assessed by magnetic resonance imaging of the forearm

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Background Endothelial function plays a key role in atherosclerotic disease. None of the currently available techniques, however, is able to visualize changes on a capillary level. T2*-weighted magnetic resonance imaging (MRI) detects changes of tissue perfusion by exploiting the BOLD (Blood-Oxygen-Level Dependent) effect. We assessed the sensitivity of BOLD-sensitive MRI in the detection of endothelium-dependent perfusion changes.
Subjects and Methods
In six healthy male volunteers (age 29±3y.) we applied a T2*-sensitive echo planar imaging (EPI) sequence (TE 17,4ms). Image data (between 3000 and 3500 images/protocol) were obtained using a pulse-trigger (TR = RR). The signal intensity changes in the forearm were assessed before, during, and after intraarterial administration of acetylcholine (Ach, 16 and 64 μg/min.) with or without previous application of L-NMMA (5mg/min.). Furthermore, Sodium-Nitroprusside was administered with a stepwise increase of the dosage from 2 to 6μg/min for 5min each. For signal intensity analysis, the contralateral arm was included as an internal reference.
Results The basal signal scatter was less than 0.2%. During acetylcholine there was a significant transient signal intensity increase at both dosages ($p<0.05$ and $p<0.01$, respectively) in the muscular tissue. In contrast, the administration of L-NMMA was associated with a significant decrease of the signal intensity ($p<0.001$). The signal increase during the ACh dose of 16μg/min. was completely blocked by previous administration of L-NMMA, whereas this effect was only partially present when applying 64μg/min. of ACh.
Application of Sodium-Nitroprusside resulted in a similar, dose-dependent, but more plateau-like vasodilatory response.
We also observed systemic variations of the signal intensity, which involved the contralateral arm, were independent of the time of pharmacological interventions in 3 of six subjects, and more pronounced related to an uncomfortable body position.
Conclusion We conclude that BOLD-MRI is well suitable for the noninvasive assessment of vasodilatory endothelial function. The advantages over established techniques may be important for future research.

P2371 Regional findings of endothelial function in the forearm as assessed by high-field BOLD-MRI

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Background Vascular endothelial dysfunction is a hallmark of atherosclerosis and its risk factors. BOLD-MRI is known to reflect changes of tissue perfusion due to the relation of the signal intensity to the ratio of oxy-hemoglobin to deoxy-hemoglobine. Since this phenomenon, the BOLD effect, is positively correlated to the magnetic field strength, measurements at high field strength seem to be advantageous. We addressed the question whether BOLD-MRI in a high-field system provides accurate and reproducible data on alterations of endothelial function.

Subjects and Methods

17 volunteers (34±4 years) were studied using a 3 T MRI system (Signa, GE Medical Systems, Milwaukee, USA). The subjects were placed in a supine position with one of the forearms lifted and put into the head coil. A two-shot gradient-echo/EPI sequence was applied (TE 20ms, effective TR 2000ms, slice thickness 10mm, field of view 160x160mm, matrix 256x256) to generate T2*-sensitive images. The signal was continuously obtained before, during and after the following interventions on tissue perfusion:

Ischemia was induced by inflation of a blood pressure cuff to at least 50mmHg above systolic blood pressure for 3 minutes with a rapid release. RH measurements were repeated twice.

ACh (30μg/min.) was continuously applied for 3 minutes into the brachial artery. In the BOLD-MRI images, the signal difference between baseline and maximum was calculated. In a subset of volunteers we assessed regional signal intensity changes in different groups of the skeletal muscle.

Results Image quality was good to excellent in all cases. RH experiments revealed a marked SI decrease (see fig. 1, middle panel) with a trend towards reaching a plateau during the last portion of the ischemic period and a steep SI increase with a significant overshoot (3.8±0.2%SE). ACh infusion led to a plateau-like SI increase, when the analysis was performed for the entire cross-sectional view. The evaluation of single muscle groups, however, showed different curve shapes with different patterns, even within the same subject in repeat studies.

Conclusion BOLD-MRI at 3 T detects pharmacological interventions on endothelial function. The finding of a regionally different, inhomogeneous regulation of skeletal muscular perfusion is surprising and requires a more detailed investigation.

P2372 TIMI frame count index successfully identifies the patients with endothelial dysfunction

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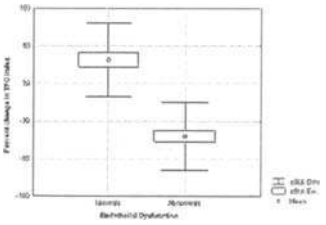
Background: Endothelial dysfunction impairs microvascular blood flow and correlates with an increased risk of vascular events. We sought to determine if a new TIMI frame count index(TFCI) could identify the patients with endothelium-dependent coronary endothelial dysfunction.

Methods: 57 consecutive patients (18 males) without obstructive coronary artery disease underwent coronary physiologic study in the Mayo Clinic were involved in the study. Coronary flow parameters were assessed using coronary angiography and a Doppler guidewire at baseline and after 0.182, 1.82 and 18.2 microgram/mL concentrations of acetylcholine (Ach) infusion. An increase in coronary blood flow >50% above baseline after 18.2 microgram/mL Ach infusion was considered to represent normal coronary endothelium dependent function. In each patient a distal landmark was defined and TFC (number of frames required for the contrast to travel from the ostium to the distal landmark) at baseline and after 18.2 microgram/mL of Ach were assessed. TFCI was defined as the vessel area divided by TFC. Percent change in the TFCI from baseline was then calculated.

Results: The mean change in TFCI was -36.1±35.7% in patients with endothelial dysfunction (n=32) and 44.6±39.3% in patients with normal endothelial function (n=25)(p<0.0001)(Figure 1). ROC curve analysis showed that a cut off value of less than 0.5% decrease in TFCI would have a specificity of 88% and a sensitivity of 87% in determining coronary endothelial dysfunction. A significant correlation was observed between the percent change in TFCI and the percent change in coronary blood flow (r=0.88, p< 0.0001).

Conclusion: Changes in TFCI in response to Ach may be used as a simple and inexpensive method for detecting coronary endothelial dysfunction.



BIOMARKERS IN ISCHAEMIA/INFARCTION

P2373 Pregnancy associated plasma protein-A levels are elevated in patients with unstable angina

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Background: Pregnancy-associated plasma protein A (PAPP-A), recently identified as an insulin like growth factor (IGF) binding protein proteinase, is a high molecular weight zinc binding metalloproteinase secreted by vascular smooth muscle cells. Increased PAPP-A activity leads to enhanced IGF bioactivity and may contribute to the progression of atherosclerosis. Thus, the current study was designed to test the hypothesis that circulating PAPP-A levels are elevated in patients (pts) with unstable angina (UA).

Methods: Blood samples were taken from 335 pts undergoing cardiac catheterization at the Mayo Clinic. PAPP-A levels were analyzed using a biotin-tyramide-amplified enzyme immunoassay. UA was defined as the new onset of anginal symptoms (<6 weeks), rest pain, or post infarction angina (within 3 weeks of infarction). Control pts were those who had coronary disease and did not meet the requirements for UA or were undergoing routine cardiac catheterization for preoperative cardiac surgery such as valve repair/replacement. Thirty-two pts with UA were identified and the circulating levels of PAPP-A were compared to the remaining pts. Clinical characteristics were identified through patient interview and chart review. Coronary angiograms were reviewed for the extent of the disease, which was defined as the number of major vessels with >70% stenosis.

Results: The study group consisted of 335 pts, 224 (67%) were males, mean age 64±11. There were no differences in the age, gender, presence of diabetes, hypertension, family history, cholesterol levels, smoking history of the pts with or without UA. The PAPP-A levels in the UA pts were significantly higher than in the pts without UA (7.1 ± 4.0 vs. 5.5 ± 3.4 mIU/L, p= 0.01, two sided p=0.036). PAPP-A levels were associated with older age (p<0.001), male gender (p=0.005) and lower levels of high-density lipoprotein (p=0.002). PAPP-A levels were not associated with the extent of the coronary artery disease.

	UA (N=32)	Control (N=303)	p value
PAPP-A level (mIU/L)	7.1 ± 4.0	5.5 ± 3.4	0.036

PAPP-A levels in unstable angina (UA) and control groups.

Conclusion: Patients with unstable angina have higher levels of circulating PAPP-A than patients without unstable angina. PAPP-A may be marker for plaque instability.

P2374 Is C-reactive protein level a useful marker of severity and infarct size in patients with acute ST elevation myocardial infarction?

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Background: Elevated C-reactive protein (CRP), a marker of chronic inflammation and an acute phase reactant, has been shown to correlate with higher risk for coronary events in patients with unstable angina. Our aim was to assess the value of CRP levels as a marker of infarct severity in the setting of acute ST-segment elevation myocardial infarction (STEMI).
Methods: Ninty-nine consecutive patients (mean age 62 ± 13, 68% men) with first acute STEMI were prospectively enrolled in the study. CRP levels were measured within 24 hours of symptoms onset by a highly-sensitive assay. Infarct size was assessed by peak creatine kinase (CK) levels and two-dimensional echocardiographic examination performed on day 2 or 3. The patients were divided into 2 groups according to their CRP levels.
Results: Patients with elevated CRP levels (>3.4 mg/dL) had more anterior infarcts, larger infarct size, worse left ventricular systolic function, higher wall motion score index, and worse Killip classification. In addition, in-hospital mortality was significantly higher in patients with elevated CRP levels (table).

Variable	CRP<3.4 mg/dL (n=72)	CRP>3.4 mg/dL (n=27)	P value
Age, y (mean±SD)	59 ± 12	69 ± 11	0.05
Men (%)	53 (73)	17 (63)	NS
Anterior MI (%)	29 (40)	17 (63)	<0.001
Killip 3-4 (%)	3 (4)	12 (44)	<0.001
Reperfusion therapy (%)	50 (70)	18 (66)	NS
Peak CK (U/l)	1792± 214	3152 ± 491	0.004
LV systolic function			
Moderately reduced (%)	9 (12)	10 (37)	0.005
Severely reduced (%)	3 (4)	6 (22)	0.005
WMS index	1.51± 0.3	1.78 ± 0.3	<0.001
In-hospital mortality (%)	1 (1)	5 (19)	0.002

MI=myocardial infarction, CK=creatine kinase, WMS= wall motion score

Conclusion: In patients with STEMI, CRP levels on admission correlate with infarct size, reduction in left ventricular systolic function, the development of clinical heart failure, and with increased in-hospital mortality.

P2375 B-type and atrial natriuretic peptide in acute myocardial infarction – impact of left ventricular function and systemic inflammatory response

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Background: Elevated plasma levels of interleukin-6 (IL-6), B-type (BNP) and atrial natriuretic peptide (ANP) are associated with an increased risk for recurrent non-fatal myocardial infarction or fatal cardiovascular event in patients with acute myocardial infarction (MI). Volume expansion or pressure overload have been postulated to be responsible for BNP and ANP secretion in MI. Also members of the interleukin-6 family are able to induce ANP expression and secretion. The purpose of this study was to assess whether the natriuretic peptide system in MI is activated in response to impaired left ventricular (LV) systolic function and systemic inflammation in MI.
Methods: In a prospective study, 45 consecutive patients presenting with MI (age 58±3 years, mean±SD) undergoing emergency angioplasty (PTCA) and 20 patients who underwent elective angioplasty (controls, age 57±4 years)were enrolled. The study design allows for a discrimination of procedural effects from MI sequelae. Plasma-BNP and -ANP was analysed for up to 7 days post MI. White blood cells (WBC)were counted. IL-6, C-reactive protein (CRP)and fibrinogen (FN) gave evidence of systemic inflammation. Creatine kinase (CK-MB) and troponin I (T) detected myocardial injury. Left ventricular systolic function (LVEF) were determined by levokardiography in standard projections (LAO 30°, RAO 60°) and left ventricular enddiastolic pressure (LVEDP) was measured.
Results: Compared to controls, BNP ($p<0.05$) and ANP ($p<0.01$) were increased in MI pre coronary intervention. BNP was negatively correlated to LVEF at any time point ($p<0.05$). ANP rose correlated to LVEDP ($p<0.05$) 4 h following PTCA ($p<0.01$) and went down to baseline by 24 hours. This increase of ANP was paralleled by a rise of IL-6. IL-6 was positively correlated with WBC ($p<0.05$), CK-MB ($p<0.05$) and T ($p<0.05$). While IL-6 went down to baseline by 48 hours, ANP rose again ($p<0.05$ vs baseline). This second peak of ANP showed a positive correlation to CRP and FN (both $p<0.01$), while there was no significant correlation between ANP and LVEDP or LVEF.
Conclusion: BNP levels measured in patients presenting with MI are related to the degree of impaired LV systolic function. The delayed increase of ANP independent of procedural effects suggest a modulation of this hormone by IL-6 in MI.

P2376 Infarct size-dependent elevation of matrix metalloproteinase 9 in the early phase of myocardial infarction

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Background: Acute myocardial infarction (MI) leads to an early inflammatory response in the myocardium that enhances tissue repair. Recent animal studies have proposed that the matrix metalloproteinases MMP-2 and MMP-9, two enzymes capable of degrading damaged extracellular matrix, are involved in this process. The role of MMP-2 and MMP-9 during myocardial infarction in humans is not known.
Methods: In a prospective study, 20 patients (pts) with proven acute MI underwent coronary angiography and thrombolysis (n=7) or transluminal angioplasty (n=13) within 6 hours after onset of symptoms. Coronary angiography after 1 week showed successful reperfusion in all pts. MI size was determined as percentage of the akinetic/dyskinetic segment of the LV circumference by levocardiography (ADS) after 1 week. Patients were grouped as large MI (ADS>25%) and moderate MI (ADS<or=25%). The plasma concentrations of MMP-2, MMP-9, and the endogenous tissue inhibitor of metalloproteinases (TIMP)-1 were determined by enzyme immunoassay on admission and after 24 hours, 48 hours, 1 week, 4 weeks, 3 months, and 6 months.
Results: MI size groups were equal in age, gender, MI localisation, and reperfusion method. MMP-2 levels remained unchanged over time in both groups. On admission, the concentration of MMP-9 was elevated significantly in large MI compared to moderate MI (195±190 ng/ml vs 78±63 ng/ml, mean±standard deviation, $P<0.01$, t-test), and returned to baseline (large MI: 18±16 ng/ml, moderate MI: 16±17 ng/ml) by 1 week after MI ($P<0.05$, ANOVA). The plasma concentrations of TIMP-1 were elevated in large MI, and remained unchanged over time. The MMP-9/TIMP-1 ratio was significantly increased on admission in both size groups (large MI: 0,24±0,24, moderate MI: 0,17±0,16) and returned to baseline (large MI: 0,05±0,03, moderate MI: 0,06±0,06) by 48 hours ($P<0.05$ for both groups, ANOVA).
Conclusion: This study shows a transient elevation of MMP-9 plasma concentration during acute MI that is dependent on MI size and returns to baseline by 1 week. Also, the MMP-9/TIMP-1 ratio is elevated in acute MI suggesting an increased enzymatic activity of MMP-9. These data suggest a pathophysiologic role of MMP-9 during the early phase of acute MI.

P2377 Heat shock protein 60 homologues in unstable angina atheroma – correlation with markers of inflammation and apoptosis

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Background: Recent studies provide evidence that infection, inflammation, immunological reactions and apoptotic events play an important role in the acuity/progression of atherosclerosis. In this respect, a chronic persistent Chlamydia pneumoniae infection, indicated by the presence of chlamydial heat shock protein 60 (cHSP 60), endogeneous human (h) HSP 60, that serves as a target for autoimmune reactions, C-reactive protein (CRP), a systemic inflammatory marker with predictive significance, and caspase 3, a cell death effector, are focused.
Methods: Coronary atherectomy specimens retrieved from 30 primary target lesions of patients with unstable angina (UA; n=15) or stable angina (SA; n=15) were assessed immunohistochemically for the presence of cHSP 60, hHSP 60, CRP and caspase 3. These data were correlated with plaque morphology and assessed for prevalence in either UA or SA lesion group.
Results: Coronary plaques revealed immunoreactive cHSP 60 in 64%, hHSP 60 in 80%, CRP in 58% and caspase 3 in 89% of the lesions vs. none of 20 undiseased control samples. Intimal predilection sites were regions with macrophages/foam cell accumulation, inflammatory infiltrates and sparse cellularity. Mean expressions were 6.6% for cHSP 60, 6.5% for hHSP 60, 1.8% for CRP and 7.8% for caspase 3. As the central finding of the present study, the expression of all four proteins was significantly ($p<0.05$) higher in UA lesions compared to SA lesions (8.7% vs. 3.0%, 8.7% vs. 2.0%, 2.3% vs. 1.1%, 10.8% vs. 3.7%). Moreover, we found positive correlations between cHSP 60/hHSP 60 ($r=0.44$; $p<0.01$), cHSP 60/caspase 3 ($r=0.43$; $p<0.01$), hHSP 60/CRP ($r=0.45$; $p<0.01$), hHSP 60/caspase 3 ($r=0.69$; $p<0.01$) and CRP/caspase 3 ($r=0.46$; $p<0.01$). Interestingly, some correlations were observed only in the UA and not SA subgroup: cHSP/hHSP 60 ($r=0.35$; $p<0.05$), hHSP 60/CRP ($r=0.34$; $p<0.05$) and hHSP 60/caspase 3 ($r=0.64$; $p<0.01$).
Conclusions: cHSP 60, hHSP 60, CRP and caspase 3 are partially colocalized within coronary primary atheroma, the most in lesions associated with UA. Thus, our data suggest a role of all four proteins as intimal determinants implicated in human coronary plaque instability.

P2378 Diagnostic implications of elevated brain natriuretic peptide levels in patients with non-ST-segment elevation myocardial infarction

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Background: Brain natriuretic peptide (BNP) reflects both ventricular stretch and neurohumoral activation and is a reliable biochemical marker in patients with heart failure, correlating strongly with haemodynamic parameters and clinical signs. The diagnostic and prognostic value of BNP in patients with non-ST elevation myocardial infarction (NSTEMI) is not known.
Methods: 98 patients (age 63 ±20 yrs, 38 females) with NSTEMI were included according to the following criteria: i. angina pectoris in the last 48 h, ii. ST-segment depression (>0.5mm) and/or negative T-waves in at least 3 leads on surface ECG, iii. positive troponin T (>0.1 ng/ml). BNP was measured with a point-of-care device at hospital admission. All patients underwent coronary angiography within 72 h and angioplasty was performed as indicated.
Results: A mean time of 8±6 hours elapsed between beginning of angina and BNP measurement. BNP levels ranged between 5-1256 pg/ml with a mean value of 127 ± 196 pg/ml. BNP levels correlated moderately with left ventricular ejection fraction (r= -0.36, p=0.01). In 58 patients BNP exceeded 80 pg/ml. 52 of these patients (89%) had at least one haemodynamic significant (>70%) stenosis of the left anterior descending artery (LAD) and/or right coronary artery (RCA) or 3 vessel coronary artery disease (CAD). Among 40 patients with BNP<80 pg/ml only 10 patients (25%) were found to have significant LAD/RCA stenosis or 3 vessel CAD. A strong association existed between BNP level and Killip-class (table).

Killip class	I	II	III	IV
BNP> 80 pg/ml	19	18	15	6
BNP< 80 pg/ml	33	7	0	0

BNP levels and Killip class

Conclusion: In patients with NSTEMI high levels of BNP (>80 pg/ml) associate strongly with haemodynamic significant stenosis of LAD/RCA or 3 vessel CAD and signs of left ventricular dysfunction.

P2379 Inflammatory markers correlate with coronary lesion morphology in patients with unstable angina

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Increasing evidence suggests that atherosclerosis is an inflammatory disease and that elevated inflammatory markers predict the risk for cardiovascular events. We sought to assess the relation between inflammatory markers and angiographic features of target coronary lesions in patients with unstable angina enrolled in the CAPTURE trial (n=853). Angiograms were evaluated by a blinded Angiographic Committee.
Results: At baseline, neopterin levels > 10 nmol/L were found in 47.3% and CRP levels > 15 mg/L were found in 41.4% of the patients. There was no correlation between neopterin and CRP concentrations (r=0.12; P=0.21). Both neopterin and CRP did not predict the presence of thrombus formation and TIMI flow at baseline. However, we observed a significant correlation between complex lesion characteristics and inflammatory marker concentrations (neopterin: r=0.85; P<0.0001; CRP: r=0.64; P<0.001). Multivariate analysis including troponin T measurements demonstrated that only neopterin was independently associated with complex lesion characteristics (P<0.001), PCI-related complications (P=0.003), and patients' short-term prognosis (death or MI at 30-day follow-up; P=0.002). At discharge, neopterin was elevated in 52.5% with a significant difference between the abciximab and the placebo group (40.3% vs. 64.7%; P<0.001). Patients with discharge neopterin concentrations < 10.0 nmol/L had a more favorable prognosis (adjusted hazard ratio 0.73 [95%CI 0.58-0.95] whereas discharge CRP levels < 15 mg/L did not predict a better outcome (adjusted hazard ratio 0.98 [95%CI 0.58-1.50].
Conclusions: Serum concentrations of neopterin and CRP, respectively, were associated with the presence of complex target lesion characteristics in patients with unstable angina. Neopterin, a marker for macrophage activity, was the more powerful predictor of patients' short-term risk and neopterin levels were reduced by abciximab treatment. Our findings suggest that neopterin may be regarded as a novel marker of plaque instabiliy.

P2380 Strong and independent association between serum interleukin 1 receptor antagonist and future cardiovascular events

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Background: Inflammatory mechanisms play a crucial role in the development and progression of atherosclerosis and plaque vulnerability. C-recactive protein (hs-CRP) is being discussed as a marker of future cardiac events. Interleukin (IL)-1 as a central cytokine is responsible for activiation of a variety of proatherogenic features andacute phase responses. We evaluated the impact of IL-1 receptor antagonist (ra) on future cardiovascular events in patients (pts) with coronary artery disease (CAD).
Methods: In 1339 pts with documented CAD inflammatory markers such as hs-CRP [mg/l], fibrinogen [mg/dl], and IL-1ra [pg/ml] were determined. 1336 pts (99.9%) had a follow up (f/u) after 4.1 (maximum 5.2) years.
Results: During the f/u 103 pts died because fo cardiac reasons, 51 pts suffered from non-fatal myocardial infarction (MI). Univariate predictors (p<0.05) for the combined endpoint were age, diabetes, HDL-cholesterol, statin treatment, interventional strategy, ejection fraction as well as serum level of hs-CRP and fibrinogen. The relative risk (RR) for increasing IL-1ra per quartile was 1.3 (95%CI 1.1-1.6) in a fully adjusted model (for adjustment see Table). hs-CRP and fibrinogen lost their predictive impact after inclusion of IL-1ra in the multivariate model.

Risk Ratios Acording to IL-1ra

	Q1	Q2	Q3	Q4
range [pg/ml]	<167.9	167.9 - 300.1	>300.1 - 505.2	>505.2
% cv event	5.4	11.0	12.7	17.1
Relative Risk	1	2.4	2.4	2.7
95% CI	–	1.7 - 4.7	1.2 - 4.6	1.4 - 5.2
P value	–	0.008	0.01	0.004

Adjusted for age, sex, bmi, classical risk factors, clinical (acute coronary syncrome, history of MI, extent of vessel disease, ejection fraction) and therapeutical (statin, betablocker, and interventional therapy) features.

Conclusion: IL-1ra is a strong and independent predictor of future cv events in documented CAD. Most interestingly, in this large prospective cohort of CAD pts IL-1ra appears superior to hs-CRP and fibrinogen.

P2381 L-arginine attenuates lymphocyte activation and anti-oxidized LDL antibody levels in unstable angina

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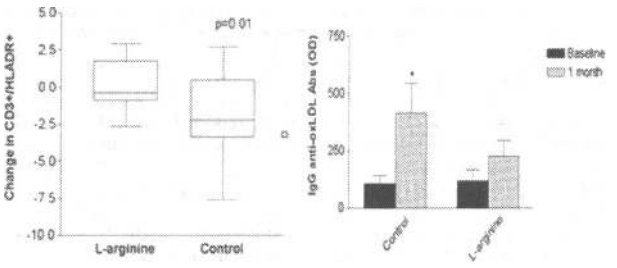
Background: Pts with acute coronary syndromes (ACS) exhibit evidence of peripheral T lymphocyte activation, elevated acute phase proteins and enhanced oxidative stress. L-arginine (Arg), a NO donor, ameliorates experimental atherosclerosis and restenosis as well as endothelial dysfunction. We studied the effect of Arg on lymphocyte activation and anti-oxLDL antibodies in pts with unstable angina (UA) undergoing PCI with stent placement.
Methods: Pts with UA were randomized to treatment with Arg (10 gm/daily; n=13) or none (n=16) for 1 month starting on day of stent deployment. Lymphocyte activation was assayed by FACS employing double staining with a common lymphocyte marker (CD3) and an activation marker HLA-DR, on the day of the procedure and 1 mth later. Anti-oxLDL antibodies were assayed by ELISA.
Results: Patients with unstable angina not receiving L-arginine exhibited a 43% rise in the percentage of activated peripheral T lymphocytes 1 month after stent deployment. Patients treated with Arg exhibited a fall in the fraction of peripheral lymphocytes bearing the activation marker. Antibodies to oxLDL rose significantly between baseline and 1 month follow up. Arg treatment significantly attenuated the rise in anti-oxLDL antibody levels.



Conclusion: Arg attenuates the systemic rise in peripheral lymphocyte activation and oxidative stress markers induced by vessel wall injury following PCI. These effects may contribute to a favorable effect of the drug in pts with ACS undergoing PCI.

P2382 Clinical significance of matrix metalloproteinases activity in acute myocardial infarction patients

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Matrix Metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are key enzymes in myocardial fibrillar collagen degradation. We investigate the effect of increased MMP-1 and their TIMP-1 activation on the left ventricular (LV) remodeling in-patients (pts) with acute myocardial infarction (AMI).
Methods: We measured MMP-1 and TIMP-1 plasma levels in 24 pts (mean age 58,46±13,9yrs) with first attack of AMI and classified in two groups. Pts with a third Heart Sound (S3) Ejection Fraction (EF)<45% and End Diastolic Diameter (EDD) of LV.>47,5mm were included in group A. In group B were pts without S3 with EF>45%and EDD<47,5mm. Plasma blood samples were collected at the time of admission in the hospital (0h) as well as, 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 3days, 4d, 5d, 7d, 15d,30d, thereafter and measured by relevant ELISA kits. All patients did not have previous history of any other disease. For statistical analysis ANOVA rp.m.a and unpaired t-test was used. Data are expressed as mean values SEM in ng/ml. $p<0,05$ was considered statistically significant.
Results a) The mean blood values of MMP-1 were found higher in-group (A) average by 30% for total time points compared to mean blood values of MMP-1 in-group (B). Additionally on several time points mean blood values difference of MMP-1 between the two groups were statistically significant $0,005<p<0,008$ b). The mean blood values of TIMP-1 in-group (A) were higher in average by 10% for total time points compared to mean values of group (B).
Conclusions: Thus the degree of collagenolysis in pts with AMI expressed by higher MMP-1 and lower TIMP-1 may be related to the infarct expansion and to late process of post-MI remodeling.

P2383 Circulating matrix metalloproteinase 2 and tissue inhibitor of metalloproteinases 1 after severe and minor acute myocardial infarction

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Background: Acute myocardial infarction (AMI) induces upregulation of vascular remodeling mechanisms subserving angiogenesis. Matrix metalloproteinase 2 (MMP-2) which promotes angiogenesis by new basement membrane deposition, as well as tissue inhibitor of metalloproteinases 1 (TIMP-1) which inhibits angiogenesis by inhibiting matrix formation, both regulate angiogenesis. Aim of this study was to compare the time-dependent alterations of both MMP-2 and TIMP-1 in a thirty day assessment following severe and minor AMI.
Methods: In 29 patients (pts) with first attack of AMI, no evidence of any other disease, divided in 2 age- and sex-matched groups, group A: pts with severe AMI, large infarct size, ejection fraction <45% and subsequent heart failure and group B: pts with minor AMI, ejection fraction >45% and normal LV function, plasma levels of MMP-2 and TIMP-1 were determined on hospital admission [mean latency from the onset of chest pain: 2±1 hours (h)] before thrombolysis (0h) and subsequently 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 72h, 4 days (d), 5d, 7d, 15d and 30d and compared to respective values of 20 age- and sex-matched healthy controls (HS).
Results: In group A, at 0h, MMP-2 and TIMP-1 levels were lower than those of HS (MMP-2: 603±43 vs 885±40 ng/mL, p=0.02 and TIMP-1: 582±74 vs 710±24 ng/mL, $p<0.04$). MMP-2 levels negatively peaked twice, at 24h (511±41 ng/mL) and on 5d (524±45 ng/mL) (in both cases $p<0.05$ compared to the respective values at 0h). TIMP-1 levels increased sharply at 6h (780±40 ng/mL), peaked at 36h (763±46 ng/mL) (in both cases $p<0.001$ in comparison to the respective levels at 0h) and declined to normal values, reaching them on 5d (672±37 ng/mL). In group B, at 0h, MMP-2 and TIMP-1 levels were also lower than those of HS (790±68 vs 885±40 ng/mL, $p<0.02$ and TIMP-1: 471±89 vs 710±24 ng/mL, $p<0.01$). MMP-2 levels negatively peaked twice, at 6h (489±29 ng/mL) and on 5d (464±63 ng/mL) (in both cases $p<0.05$ compared to the respective values at 0h). TIMP-1 levels gradually increased, peaked on 5d (928±26 ng/mL) ($p<0.02$ in comparison to the respective levels at 0h) and sharply declined thereafter to normal values, reaching them on 15d (719±60 ng/mL)
Conclusions: Later alterations in MMP-2 levels and earlier elevation in TIMP-1 levels, observed in severe AMI, compared to those observed in minor AMI, may reflect delayed extracellular matrix-associated angiogenesis. Since this process is vital to initiate wound healing and could limit tissue damage, such a delayed angiogenesis may reduce myocardial salvage in the border zone after a severe AMI.

P2384 The clinical significance of circulating levels of granulocyte/macrophage-colony stimulating factor in acute myocardial infarction patients

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Despite recent advances in our understanding of ischemia-induced angiogenic process, the occurrence of vasculogenesis, i.e. the in situ formation of blood vessels from circulating endothelial progenitor cells or hemangioblasts, due to ischemia, remains an unsettled issue. Therefore, we investigated the role of granulocyte/macrophage- colony stimulating factor (GM-CSF), a hemopoietic agent with vasculogenic properties, in acute myocardial infarction (AMI) patients.
Methods: 29 pts with first attack of AMI admitted and thrombolysed during the acute phase,and no previous history of any other disease, were examined for plasma levels of GM-CSF, measured by ELISA, and compared to corresponding levels of 20 normal controls (NC) with mean values:3,1 ± 0,28 pg/ml. All pts were divided in 2 sex and age-matched groups. Group A: 15 pts with minor AMI, EF>45% and no subsequent LV dysfunction. Group B: 14 pts with large infarct size, EF<45% and residual heart failure.Plasma samples were collected at the time of hospital admission (0 hours) and 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 3 days, 4d, 5d, 7d, 15d and 30d thereafter.
Results: Data is expressed as mean values±SEM in pg/ml. For the statistical analysis the Wilcoxon test was used with a statistical significance of $p<0,05$ compared to corresponding values of: a) NC(*), b) the relevant lowest plasma value at 24h(°). Group A exhibited a slight non significant GM-CSF increase (3,92±0,83) on admission, followed by a gradual decrease reaching the lowest plasma value at 24h (2,87±0,42) which is reversed leading to a late significant peak at 5 days (10,72±1,93*°). In contrast, group B developed a significant initial peak (8,56±1,44*°) succeeded by a gradual decrease reaching a nadir at 24h (2,98±0,32) followed by a slight non significant peak at 7 days (4,08±1,25).
Conclusions: Both groups developed high initial GM-CSF levels but only in group B this increase was significant compared to NC and the lowest plasma value at 24h. This early increase in group B may account for macrophage recruitment leading to macrophage- induced LV dysfunction in the early post- AMI period and is later reversed in both groups. A late GM-CSF rebound at 5d is significant only in group A probably implying that vasculogenesis is enhanced, thus preserving LV function and exerting a cardioprotective potential in these pts, while it remains practically absent in those pts with extensive AMI, thus resulting in LV decompensation. This study provides an important proof of concept for the key role of GM-CSF in the short-term LV remodeling following AMI.

P2385 Validation of a novel blood test for ischaemia during percutaneous coronary intervention

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Introduction: N terminal modification of albumin has been proposed as a biochemical test for the detection of ischaemia which can be used in combination with myocyte necrosis markers such as troponins. Validation of this test is difficult as there is no gold standard for ischaemia and animal models are of limited value.
Objective: We have examined dynamic changes in N terminal albumin, assessed by the ischaemia modified albumin (IMA) test in patients with induced ischaemia during percutaneous coronary intervention (PCI).
Methods: 60 patients with stable angina undergoing PCI with elective stenting (48 male, age range 38-76, median 57 years) and 28 controls with stable angina undergoing diagnostic coronary angiography (21 male, age range 38-81, median 58 years) were studied. Blood samples were taken pre-procedure, immediately post procedure, at 6 hours post procedure and 24 hours post procedure. Serum was separated and stored frozen at -80°C prior to analysis. Samples were defrosted and analysed for N terminal albumin content by cobalt binding (IMA test, Ischaemia Technologies) and for cardiac troponin I (cTnI) by a reformulated sensitive technique (ACCESS Accu cTnI, Beckman-Coulter). Baseline values were compared with post procedure, 6 hour and 24 hour values (Wilcoxon).
Results: There was no difference in IMA value at baseline between the PCI group and control (angiography only) group. In the immediate post procedure samples, values were slightly elevated in the control group (P=0.04) but markedly elevated in the PCI group (P=0.0002)compared with baseline. At 6 hours, the elevation remained significant in the PCI group (P=0.004). IMA values returned to baseline 24 hours following PCI. This pattern was observed even in patients without any evidence of peri-procedural myocyte necrosis indicated by undetectable cTnI at 24 hours. PCI to the left anterior descending artery (LAD) produced a significantly larger immediate rise in IMA than circumflex or right coronary artery PCI (P=0.01). This result may reflect the greater myocardial mass subtended by the LAD.
Conclusion: Myocardial ischaemia induced by PCI can be detected by the IMA test.

P2386 Implementation of diagnoses and outcome by chest pain unit management in the emergency department of Florence

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Background: Chest Pain Unit (CPU)-management is a valuable tool for recognizing patients (pts) with chest pain (CP) at "high-intermediate-risk" from those at "low-risk" of cardiac events (CE). However, in welfare health systems, the feasibility and potential benefits of such management in the Emergency Department (ED) require further investigation. Methods and Results. A total of 13,762 consecutive pts with CP were screened during 1998-2000. "High-intermediate-risk" pts (n=9,335) were triaged as follows: 2,420 pts with acute myocardial infarction (25,9%; 10.6% in-hospital mortality), 3,764 pts with unstable angina (40,3%; 1.1% mortality), 129 pts with aortic arch dissection (1.4%, 23,3% mortality), and 408 pts with pulmonary embolism (4,4%; 27,6% mortality); moreover 268 pts had pneumothorax (2,9%; 1,1% mortality); 90 pts had acute pericarditis (1.0%; no deaths); and 2,256 pts showed chronic coronary artery disease (CAD) associated to other conditions of clinical instability (24,2%; 5,2 mortality). "Low-risk" pts (n=4,427) were triaged as follows: 885 pts (20%) were recognized as having CAD (1.1% mortality) by observation and/or serial ECG or stress-tests in CPU; 2,672 pts (60%) were discharged <6 hours after a negative first-line evaluation, including ECG, troponins and echocardiogram (echo), (0.2% no fatal CAD at 6 month follow-up); 870 pts (20%) were discharged <24 hours after further negative investigation, including serial ECG, echo, myocardial scintigraphy, exercise tolerance test; none of these pts had fatal/non fatal CAD at follow-up. Among these low-risk pts in whom CAD was excluded, 52% were diagnosed as having anxiety or gastroesophageal disorders as follows: 27% had active gastroesophageal disorders (17% peptic ulcer and 10% esophageal reflux or spasm), and 25% had anxiety (9% panic). Conclusions. An effective screening program with an observation area (CPU) inside the ED was successfully implemented in a public health environment and contributed significantly to reduce admissions (80% early discharge from the CPU-ED), and in "low-risk" pts, to recognize CAD in 20% of pts avoiding inadvertent discharge. Moreover, in one half of "low-risk" pts CPU management allowed recognition of alternative causes of chest pain.

P2387 Early risk stratification in ST-segment elevation myocardial infarction with admission troponin T and ST-segment resolution

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The prognostic value of admission troponin T (tnT) levels and the resolution of the ST-segment elevation in ST-elevation myocardial infarction (STEMI) is well established. However, the combination of these two early available markers for predicting risk has not been evaluated. The aim of this study was to evaluate the combination of admission tnT and ST-segment resolution (ST res.) for early risk stratification in STEMI patients treated with thrombolysis.

Methods: Plasma-tnT was determined on admission with the third gen. assay on an Elecsys in 881 patients with STEMI from the Assent 2 and Assent plus studies. ST-segment monitoring for analysis of ST res. was performed in 752 patients from the same studies. 516 patients had both admission tnT and ST-segment monitoring. All patients were followed for one month regarding mortality. We used a prospectively defined cut-off value of tnT of <0.1 μg/L or >=0.1 μg/L. For ST res., <50% or >=50% measured after 60 minutes was used as cut-off.

Combining these two markers a profound difference in risk (R.R. 22.7, 95%CI 3.0-174.2) was observed between the high (tnT >=0.1 μg/L and ST res.<50%) and low (tnT<0.1 μg/L and ST res. >=50%) risk groups.

Results:

Results:	tnT			ST res.		
	<0.1ug/L n=400	≥0.1ug/L n=116	p-value	≥50% n=215	<50% n=301	p-value
Death 30 days	2.0%	9.5%	<0.001	0.9%	5.6%	0.005

Death 30 days	tnT<0.1ug/L	tnT ≥0.1ug/L	p-value
ST res.≥50%	0.6% (n=177)	2.6% (n=38)	for trend
ST res.<50%	3.1% (n=223)	12.8% (n=78)	<0.001

Conclusion: Especially elevated tnT (>=0.1 μg/L), but also no ST res. (<50%), were associated with an increased 30 day mortality. ST res. (>=50%) identified a large low risk group of patients. The combination of these two markers gave additive early information about prognosis and further improved the risk stratification.

P2388 Prognosis in patients with troponin positive acute coronary syndrome without electrocardiographic abnormalities

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Background: Prognosis in unstable angina (UA) and myocardial infarction (MI) correlates well with the extent of cardiac troponin release into peripheral blood in the hours and days following hospital admission. This is additive to the prognostic information available from electrocardiography (ECG). Little is known about the significance or otherwise of troponin positivity in the context of normal electrocardiographic appearances. We performed a prospective, observational, outcome study of patients admitted to our hospital with chest pain associated with an elevation in serum cardiac troponin I but normal ECGs.

Methods: All cases of admission to our acute cardiac and coronary care units over a 1-year period because of suspected MI or UA were identified and followed for the course of their admission. The only inclusion criterion for further follow-up was an elevation of serum troponin during hospital stay. Patients whose ECGs were abnormal and who had been enrolled previously were excluded.

Results: Out of 2098 patients screened, 102 (4.9%) satisfied the study entry criteria. The 30-day mortality and non-fatal MI rates were 1.0% and 2.0% respectively. At one year, these had increased to 3.0% and 3.0%. All 3 deaths at one year were from non-cardiac causes.

Conclusion: In this relatively small study population, troponin positivity, in patients admitted with suspected UA or MI, in the presence of normal serial ECGs was not associated with adverse cardiovascular outcome. Larger studies are warranted.

P2389 Markers of myocardial injury following coronary artery bypass surgery

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Aim: To assess the clinical significance of serum cardiac troponinT (cTnT) assay in detection of perioperative myocardial infarction (PMI) after coronary artery bypass grafting (CABG).

Methods: The clinical utility of cTnT was compared to that of total CK, CKMB mass, CKMB activity and myoglobin. Serial venous blood samples were obtained before surgery and 4, 8, 16, 24, 48 and 72 hours after aortic unclamping (AU) in 42 patients who underwent CABG. We had 6 PMI patients, 24 patients with minor myocardial damage (MMD) and 12 without ischemic myocardial changes (no IMC).

Results: In discriminating no IMC from PMI, diagnostic sensitivity, specificity and predictive values of cTnT was superior to that of CKMB mass, CKMB activity, myoglobin and total CK during 72 hours after AU. However, in discriminating MMD from PMI the diagnostic performances for CKMB mass and CKMB activity was superior to that of cTnT during first 24 hours. After 24 hours diagnostic performances for cTnT was improved, but began to decline for CKMB isoenzymes. Discriminator power of myoglobin measurements was lower than that of cTnT and CKMB mass.

Conclusions: Our results indicate that the troponin T is an accurate marker for detection and monitoring of perioperative myocardial damage, especially 24 hours after AU.

P2390 Short-term outcome and its predictors in patients with acute chest pain and normal troponin I levels

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Background: The benign prognosis of patients with acute chest pain and normal Troponin levels is controversial.
Method: The study group consisted of 301 consecutive patients evaluated in the emergency room for acute chest pain with normal troponin I levels (determined upon arrival, and 8 and 12 hours after pain onset). Clinical (chest pain score and risk factors) and ECG data were collected. Sixty-eight patients were discharged early (<24h) after exercise testing and followed-up 10 days later. Outcomes (recurrent angina (RA), acute myocardial infarction (AMI) and cardiac death (CD)) were recorded in all patients during hospital admission or on an ambulatory basis in patients discharged early.
Results: Cardiac ischemia (abnormal exercise testing or angiogram) was seen in 93 (31%) patients, RA in 34 (11%), AMI in 7 (2.3%), CD in 4 (1.3%) and major events (AMI or CD) in 10 (3.3%). By multivariate analysis, the predictors of a diagnosis of cardiac ischemia were: male sex (OR=2.7; CI=1.3-5.6; p=.006), age ^{3}64 (OR=2.5; CI=1.3-4.9; p=.008), at least 2 concomitant major risk factors (OR=2.8; CI=1.4-5.4; p=.003), and chest pain score >10 points(OR=3.5;CI=1.8-6.7; p=.0002). RA was associated to insulin-dependent diabetes (OR=3.5; CI=1.1-12.2; p=.04), coronary by-pass surgery (OR=6.0; CI=1.5-25; p=.01), chest pain score >10 points (OR=9.9; CI=2.3-44; p=.003) and ST segmentdepression (OR=3.3; CI=1.3-8.4; p=.01); AMI to insulin-dependent diabetes (OR=12;CI=2.5-59; p=.008); CD to age >72 (OR=3.1; CI=2.7-3.7; p=.01); and major events to insulin-dependent diabetes (OR=11.4; CI=2.9-45; p=.002).
Conclusions: In troponin-negative chest pain, cardiac ischemia can be evidenced in at least one-third of patients, and the rate of cardiac events is not negligible. Clinical and electrocardiographic data should be carefully evaluated in this population.

P2391 Value of cardiac troponin I as a sole marker of risk in acute coronary syndromes

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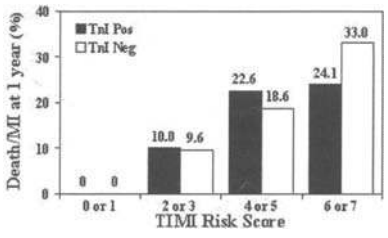
Background: Cardiac-specific troponins (Tn) were shown to be powerful independent predictors of future cardiac events in patients (Pts) with non-ST segment elevation acute coronary syndromes (ACS). Nevertheless, its prognostic value is sometimes overestimated.
Objective: We sought to evaluate the prognostic value of TnI, as a sole marker of prognosis, in Pts with ACS, using the TIMI Risk Score (RS) in Pts with elevated (TnI Pos) and normal (TnI Neg) levels of TnI.
Methods: We studied 433 consecutive Pts admitted to our Coronary Unit with ACS (mean age 63 ± 11 years, 21% female). Pts were classified according to the highest level of TnI measured during the first 24 h, using the cut-off value of > 0.1 ng/ml for TnI Pos. The 7 variables of the TIMI RS were applied at admission and the study endpoint was the combination of death or myocardial infarction (MI) at 1 year.
Results: TnI Pos was found in 239 Pts (55.2%). The incidence of death or MI at 1 year was 16.7% in Pts with TnI Pos and 11.3% in TnI Neg (p=0.053). The incidence of death or MI at 1 year, according to the TIMI RS in Pts with TnI Pos and Neg were as follows:
In Pts with TnI Pos the incidence of death or MI at 1 year was 8.2% in Pts with a TIMI RS < or=3 and 20.57% in Pts with a TIMI RS>3 (p<0.05). In Pts with TnI Neg the incidence of the study endpoint was 7.6% in Pts with a TIMI RS < or =3 and 15.7% in Pts with a TIMI RS>3 (p<0.05).



Death or MI according TIMI risk score.

Conclusion: Troponin I should not be relied on as the sole marker for risk stratification in patients with ACS, because either patients with positive or negative troponin I levels presented a wide range of risk of death or MI at 1 year. In clinical practice, multiple variables should be integrated into a global assessment of risk.

P2392 The kinetic properties of troponin I release during small myocardial infarctions

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Rationale: Cardiac troponins are nowadays considered the preferred markers for the diagnosis of myocardial infarction, according to the new definition (ESC/ACC). The kinetic of their blood release during classical myocardial infarctions is characterized by a relatively early appearance after chest pain onset and a rather long persistence in the blood (days-weeks). On the contrary, little information is available on the kinetic properties of the release of these markers during small or minimal ischaemic damage. This may have clinical impact on the correct planning and timing of marker-based protocols for chest pain evaluation in the emergency departments.
Methods: According to the methodology approved by the ESC/ACC joining group, the decisional level for troponin I in our hospital was set at 0.13 ng/ml. Small myocardial infarctions were defined as those with peak troponin I blood level between 0.13 and 0.1 ng/ml. The diagnosis for myocardial infarction comprised also chest pain characteristics and/or ECG changes according to the classical WHO criteria.
Results: In the year 2000 troponin I was measured consecutively in 2657 patients with suspected acute coronary syndrome. This has been confirmed in 760 patients (28.6%). After exclusion of patients with inadequate or incomplete values of cardiac markers (less than 3 measurements and immediate decrease values) we evaluated 134 patients, 120 of whom with a peak value less or equal to 0.1 ng/ml (group A) and 14 with peak values greater than 0.1 ng/ml (group B). The average time to peak was 7.4(4.1) hours in the group A and 8.8(4.9) hours in the group B (p=0.01). The normalization time was 18.5(14.5) hours in group A and 144.9(73.3) hours in group B (p<0.001). In the group A the normalization was achieved after 12 hours in 49 patients (40.8%), after 18 hours in 42 patients (35%), after 24 hours in 21 patients (17.5%) and after 48 hours in 8 patients (6.7%).
Conclusions: the kinetic properties of troponin I blood release after myocardial infarction is variable, particularly in relation to the ischaemic extent. This finding has to be taken into account in the planning of diagnostic protocols for rapid triage of patients coming to the emergency department for chest pain

P2393 A multimarker strategy for the risk stratification of unstable angina using C-reactive protein, troponin T and myoglobin

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Background: Cardiac markers have different release characteristics and varying sensitivity/specificity. A multi-marker strategy testing for several prognostic markers may improve risk stratification in patients with non-ST-elevation acute coronary syndromes.
Methods: This prospective multicenter cohort study included derivation(n=1000) and validation sets (n=500) of consecutive patients admitted with non-ST-elevation acute coronary syndromes. Single assays of 3rd generation troponin T(TnT),high sensitivity C-reactive protein (CRP)and myoglobin (Myo) were performed after a median time of 9 hours from symptom onset.All results were kept blinded until the conclusion of the study. The association between all markers and 180-day events was examined by chi-square and Cox regresion analyses. The primary endpoint was the 180-day incidence of the composite of death or myocardial infarction(D/AMI).
Results: D/AMI occurred in 9.5% of patients at 180 days. Cox multivariate analysis identified the following independent variables (see Table). The addition of CRP,Myo and TnT values to the clinical model increased the area of the receiver-operator (ROC)curve from 0.66±0.03, to 0.67±0.03, 0.67±0.03 and 0.72±0.03, respectively. When all three markers were added, the ROC area increased to 0.745±0.03(p<0.03).This results were confirmed in the validation set(area of the ROC curve 0.72±0.03, p=0.43)

	chi-square	Hazard Ratio	95% CI	p
TnT>0.1 ng/ml	30.2	2.31	1.50-3.60	0.0001
Age(per year)	28.9	1.03	1.01-1.05	0.003
CRP >3 mg/L	8.6	1.97	1.23-3.16	0.005
ST segment depression>1mm	7.7	1.71	1.09-2.70	0.009
Prior angina	5.4	1.71	1.13-2.60	0.024
Myo > 80 ng/ml	5.3	1.70	1.09-2.80	0.037

Conclusions: In a non selected population of non-ST elevation acute coronary syndromes, a model including 3 cardiac markers enhanced the predictive performance of clinical predictors.A combination of these markers may assist to the identification of patients at increased risk of future events.

NURSING ROLES IN HEART FAILURE MANAGEMENT: MEETING THE NEEDS OF PATIENT AND CARERS

P2394 Factors causing hospitalisation due to heart failure

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Aim: to determine delay time and factors causing hospitalisation in patients with heart failure and to assess the levels of knowledge and self-care behaviour.
Material and method: A consecutive sample of patients with chronic heart failure in NYHA II-IV, hospitalised at one university and one county hospital in Sweden were included in the study. Data were collected through structured, standardised interviews with the patients and through chart review.
Results: Of the 163 patients surveyed, mean age was 78 years, 47% were females, 69% suffered from ischemic heart disease and 27% had diabetes. At time of admission 58% of the patients were in NYHA III-IV, 47% had atrial fibrillation, 58% received an ACE-inhibitor, 81% diuretics and 55% beta-blockers. The most common symptoms at admission were dyspnea (92%), fatigue (67%), ortopnea (50%), leg or abdominal oedema (48%) and chest pain (30%).
The initiative to seek care came from the patient in 36% of the cases, from the family in 22% and 27% were referred by their GP. Delay in seeking medical assistance was analysed showing that 19% of the patients sought care during the same day as their symptoms first occurred, 33% within one week, and almost half of the patients delayed more than 1 week.
The most common reason for the deterioration of heart failure was myocardial infarction or acute anginal chest pain causing 28% of the hospital admissions. Not optimal treatment was the primary cause of hospitalisation in 21,5% and noncompliance, infections and arrhythmias in 12% respectively.
Approximately 60% of the patients did not know the rationale for weighing themselves daily and only 23% performed daily weighing. Half of the patients did not plan to take any action if they noted signs of fluid retention and only 26% had knowledge on flexible diuretic intake. Half of the patient recognised the importance of fluid restriction, but only one third restricted their fluid intake. Half of the patients exercised regularly and 90% took an influenza immunisation every year.
Conclusion: Treatment-seeking delays for heart failure symptoms are high with one third of the patients waiting for more than 2 weeks after symptom onset. Most common factor causing hospitalisation were myocardial infarction or angina. Optimised heart failure treatment and improved compliance may prevent one third of the hospitalisations. Knowledge and self-care were insufficient. Patient education and other interventions in order to improve knowledge and self-care behaviour need to be improved.

P2395 Searching for underlying mechanisms in nurse led heart failure management

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Background There is an increasing body of knowledge on non pharmacological nurse led heart failure (HF) management programs. In addition to the effectiveness of these programs, it is vital to know what the mechanisms of effects are, e.g. improved patient compliance, early recognitions of deterioration or/and improved self-control of patients.
To determine the role of underlying mechanisms of a non pharmacological nurse led HF management program, a multicenter study recently started. (Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure: COACH).
In this study 1050 patients with advanced HF, older then 18 years of age will be randomised into 1) care-as usual or 2) a low intensity HF management program or 3) a high intensity HF management program. Patients will be recruited from 10 centres in the Netherlands and patients will be interviewed at their initial admission to the hospital, and at 1, 6, 12 and 18 months after discharge. In addition to the main study on mortality, readmission, costs and quality of life, 4 projects are initiated to look at underlying mechanisms
1. What is the reason for readmission of patients. Data of all readmitted patients and their partners (if available) in the study will be collected from medical chart, interview and data from health care providers. A profile of high risk patients for readmission will be produced.
2. What are the knowledge, attitude and skills of patients with or without a HF management program? (Questionnaires)
3. How do patients from the three groups take are for themselves? (European HF Self-care Behaviour Scale).
4. How do patients from the three groups comply with the regimen? Compliance will be assessed by using a microprocessor-based medication monitoring (medication container with a microprocessor) self-report, diaries and blood-samples. Qualitative data will be collected on in a subsample on perception of a complex medical regimen
The study started in January 2002 and is planned be completed in 2005. Data on mechanisms underlying effectiveness of nurse led HF management can help to improve HF care and adapt existing or develop new programs for HF patients.

P2396 A study of medication self management during heart failure: the importance of support for both patient and carer

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Introduction: Patients with heart failure (HF) should take a range of medications that can reduce mortality, morbidity and the need for re-hospitalisation. Though compliance with prescribed treatments is vital to realise the benefits of these drugs, comparatively little is known about how those with HF approach medication management when at home nor the roles that carers have in management.
Method and Results: A qualitative interview approach was used to examine medication management in 50 patients with NYHA class II & III HF (33 males, average age 68 years; 17 females, average age 67 years) and 30 of their carers. Patients were recruited from the out patient clinics of two large hospitals in an urban area of Scotland. HF patients took a mean of 9 different medications per day (SD 4.3, range 4-21). Drugs taken most commonly included loop diuretics (n=38), ACE Inhibitors (n=38), beta blockers (n=17) and Warfarin (n=14). 28 (93%) of the 30 carers reported being involved daily in managing the medication. This assistance ranged from reminding individuals to take their medications occasionally to organising all aspects of medication provision and management. Carers involvement in management also tended to increase with patients in class III HF. Those with HF and the carers saw the medication as being important but both groups had very limited knowledge of why this was case or the specific purpose of each drug. Both groups reported receiving little support from health professionals in relation to medication management. Despite these limitations, carers and patients collaborated to develop sophisticated ways of coping with the dangers they associated with the medications. To lessen these dangers, they utilised home made pill-boxes (33%), commercial boxes (33%) or the medications' original containers (33%). Each method was selected based on the perceived capabilities of those with HF, the dangers associated with medications and the need that was perceived to live a normal life.
Conclusion: Knowledge of the medications and their management was poor in both those with HF and their carers. Carers played a pivotal role in the management of HF medications. Though both parties received little support from health professionals, they collaborated to develop ways of managing the medications. In addition to providing greater support to those with HF, health professionals should involve carers in education and support related to the management of HF and work in partnership with both parties to identify the best means to manage medication-taking effectively.

P2397 Six first months of a new heart failure unit: nurse evaluation of patients

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Knowledge about heart performance, heart failure (HF) and treatment (T) can help patients (P) to be more compliant and have better self care (diet, weight control, smoking or alcohol habits, etc). In order to know how much P know about their disease and their T, and how compliant they are, we designed a short nurse questionnaire, composed of 14 items addressed to several aspects of knowledge and understanding of heart performance and HF, treatment, weight and blood pressure control, diet, physical activities and smoking and drinking habits.

Results: 173 P (mean age 65.6 years) have been evaluated since august-2001 at the first visit to the HF unit. Only 63 P (36%) know and understand the performance of the heart. Only 62 P (36%) understand the disease. 145 P (84%) know more than 3 alarm signs of worsening. Only 74 P (43%) know all the names of the pills they are receiving, although 122 (70%) know at least about 3/4 parts of them. Only 52 P (30%) know the action of all the pills they are receiving, although 118 (68%) know at least the action of 3/4 parts of them. 94% of P say they are taking all the medication prescribed. 162 P (94%) carry on always their written prescription and only 2% never do this. 56% of P control weight only at the medical visit and only 19% control weight more than once a week. Only 31 P (18%) control blood pressure more than once a week and 45% of P control blood pressure only at the medical visit. Only 76 P (44%) say to always follow a restricted sodium diet, although 80% of P say to follow it always or almost always. While only 9 P (5%) do some kind of physical exercise, the majority of P (83%) do walking and daily life activities. 94 out of 107 P with ischemic heart disease (88%) know how to use sublingual nitroglicerin. The great majority of P never smokes (91%) and never or only very rarely drinks alcohol beverages (87%).

When analysed by age (>69 versus <70 years) we found statistical significant differences in only 4 items: knowledge and understanding of heart performance and HF, knowledge of action of the pills they are receiving and physical activities.

Conclusion: there is a lot of work to do in nurse-guided education of P with HF, although T compliance, alarm signs, use of nitroglicerin and abstinence of smoking and alcohol intake seems to be initially quite assumed by the majority of our P. Results do not differ in the majority of items among elderly and younger P, except in several aspects of knowledge and understanding of disease and treatment, and in physical activities.

P2398 Delivering evidence-based care to patients with heart failure: impact of a nurse-delivered programme in 9 UK centres

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The evidence base for the management of heart failure is well established but implementation of the evidence into routine practice is often slow and variable across the health service. Consequently, heart failure has been identified by the UK Government as a target area for service improvement. OMADA is a unique secondary-care based nurse-delivered patient-management programme designed to improve the delivery of evidence-based care (including patient education, lifestyle advice and drug therapy). We describe the impact of this programme on the prescription of drug therapy known to improve prognosis in nine UK centres. Methods: Trained specialist nurses were appointed in the 9 hospitals in 1999. Heart failuire patients were identified from local disease registers, an audit, and new referrals. These patients were managed by the nurses according to an agreed protocol supported by an electronic disease management database. 1118 patients were enrolled over an 18 month period (mean age 67 years, 73% male, 62% NYHA Class II or III), and data were entered at the time of each patient contact. These data include all the audit points recommended by the UK Health Department. Results: At entry into the programme 80% of patients were taking an ACE inhibitor but only 34% of these were taking the dosage used in clinical trials. This rose to 47% after completion of the programme ($P<0.001$). 24% of patients were taking a beta-blocker at entry to the programme (usually because of co-existent CAD). The nurses introduced beta-blockade therapy to all patients who were eligible. Carvedilol accounted for the majority of prescriptions: 29% reached the optimal dose of 25mg bd, 29% stopped the drug because of side effects, and the remainder are currently in the process of titration. Conclusions: A nurse-delivered protocol-driven heart failure management programme has been demonstrated to improve the delivery of evidence-based care (including drugs known to improve prognosis) to heart failure patients in a range of secondary care settings in the UK. This may prove a useful model for other countries.

P2399 The importance of a heart failure nurse in tailoring medication for CHF-patients

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Background: The importance of optimal medical therapy for CHF-patients has been well demonstrated. This includes high dosing of ACE-inhibitors and the institution of beta-blockade. Optimizing this medication involves intensified follow-up and guidance of these patients. A specialized heart failure nurse can play an important role in this.

Methods: During 2000 and 2001 a heart failure nurse has been involved in the care of all CHF-patients being admitted at the cardiology department of the Rijnland Hospital. Apart from giving extensive information to patients and family about their disease and its practical consequences, the nurse was used to guide medical therapy. During this time-interval characteristics of all admitted CHF-patients were collected. Furthermore both medication on admission and discharge were noted and compared.

Results: Totally 313 patients were admitted at least once in 2000 and 2001. Of the first admission 51% were men, mean age was 75 years. Mean LVEF was 42%. In 61% an ischemic cause for heart failure was present. Admission medication included an ACE-inhibitor in 38% and a betablocking agent in 22%. On discharge 44% received a betablocking agent and 72% an ACE-inhibitor. mean dose of respective medication is shown in the table.

Medication	Mean admission	Mean discharge
ACE-inhibitor		
enalapril	15mgr (n=42)	24 mgr (n=39)
captopril	48 mgr (n=44)	67 mgr (n=113)
quinapril	15 mgr (n=10)	23 mgr (n=37)
Betablocking agent		
carvedilol	15 mgr (n=15)	15 mgr (n=68)
metoprolol	85 mgr (n=12)	69 mgr (n=17)
metoprolol oros	117 mgr (n=27)	88 mgr (n=32)

Conclusion: Optimal medication for CHF-patienst has been shown to be an important contributing factor to prevent mortality and readmissions. However optimal dosing of this medication presumes intensive guidance. As shown a heart failure nurse can play a role in installing essential therapy in giving ACE-inhibitors and betablocking agents in this group as demonstrated by majority of patients receiving this medication in optimal dose.

P2400 Nurse specialist participation in a Portuguese heart failure clinic: cost evaluation

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Background: Nurses can play a very important role in heart failure (HF) clinics by helping in the implementation of current guidelines for the treatment of heart failure and by enhancing patient compliance regarding medication, diet and exercise programs. These programs of HF team management showed to be effective in improving quality of life and functional status and reducing hospital readmissions. However the costs associated with such programs are unknown in Portugal.

Aim: We evaluated the costs involved in the work developed during one year by a HF specialist nurse in an outpatient HF clinic of the cardiology department of an university hospital.

Methods: We evaluated the costs involved in the regular patient care during the weekly 4 hours-period of the clinic activity. We also evaluated the costs involved in the nurse participation in the clinical research activity developed at the clinic during a weekly 2 hours-period: during 2001, 22 patients (pts) participated in a randomised multicentric international trial involving 5 visits/pt during the first month of follow-up and a visit every 3 months thereafter.

Results: A) costs associated with clinical investigation: 1. time spent per visit and per pt: a) management of visits' agenda: 5 min; b) blood samples processing: 10 min; c) Haematology and blood chemistry results processing: 5 min; d) patient evaluation (evaluation of symptoms and vital signs, and of therapy, diet and exercise program compliance; urine dipstick; education): 10 min; total time per visit/pt: 30 min. 2. Total of visits per year = 119. Total hours/year = 59h 30 min. 3. Cost/hour = 15 Euro. Cost/year = 892 Euro. B) costs associated with regular patient care: 1. time spent per visit and per pt: a) patient evaluation: 10 min; 2. Total of visits per year = 787. Total hours/year = 131h 10 min. 3. Cost/hour = 15 Euro. Cost/year = 1963 Euro. C) Total of costs: 892 + 1963 Euro = 2855 Euro.

Conclusion: Nurse involvement in a HF clinic activities, including the participation in a tipical randomised multicentric international HF trial, is associated with moderate costs. They seem fairly acceptable since these kinds of programs showed to reduce hospital readmissions which are the main economic burden associated with heart failure.

P2401 Multidisciplinary team in heart failure outpatients at high risk of hospital readmission: benefit of combined hospital and home-based care

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Background: Hospital admission for chronic heart failure (CHF) is a major health emergency. We sought to determine whether a multidisciplinary outpatient management program decreases hospital readmissions and mortality over a six-month period.
Methods: 81 patients hospitalised with CHF at increased risk of hospital readmission were randomised to a multidisciplinary program or usual care. An hospital cardiologist and a CHF nurse evaluated each patient and made recommendations to the patient before randomisation. The intervention team included 4 cardiologists and 4 medical doctors from Internal Medicine Dept, 9 CHF nurses, and the patient's general practitioners. Contact with the patient was on a pre-specified schedule, and included a programme of hospital visits, regular phone call at home; in case of NYHA functional class III and IV patients also home visits by specialised nurses were planned. At each telephone calls or home visit, the CHF nurse performed a questionnaire to the patients to monitor the adherence to the therapy and for the early detection of symptoms and signs of clinical deterioration. The general practitioner of each patient was fully involved in the planning of patient care and kept informed of any change in clinical conditions. Patients in the non-intervention group were followed as usual. The primary outcome was the composite of the number of CHF hospital admissions and deaths over six months, compared by using a log transformation t test by intention-to-treat analysis.
Results: The median age of the study patients was 73.7 years, and 44.5% were women: the 41 patients randomised to the multidisciplinary care did not differentiate in terms of age, sex, medication, NYHA functional class, peak O2 consumption vs. those patients under control therapy. However there were fewer CHF hospital admissions (13 vs. 20) and deaths (2 vs. 4) in the intervention group vs. the control group ($p = 0.05$). The quality-of-life score, percentage of patients on target vasodilator beta-blockade agent therapy and percentage of patients compliant with diet recommendations were significantly better in the intervention group.
Conclusions: This study demonstrates that a six-month, multidisciplinary approach to CHF management can improve important clinical outcomes in recently hospitalised high-risk patients with CHF.

P2402 Reduction of readmission rate by a novel outpatient program in heart failure patients: combination of outpatient clinic and home nurse

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Background: We compared the influence of a heart failure (HF) outpatient clinic associated with a HF nurse specialist (special outpatient care,"SOPC") with conventional outpatient care ("COPC") on readmssion rate and length of stay (LOS) due to HF in a randomized study. Methods: 112 HF patients (mean age: 68±12 years, 63% males) who were hospitalized 3 months prior to study entrance were randomized to SOPC (n=48) or COPC (n=64). In all 112 patients an individual prescription of RAAS antagonists and additional betablockade including an uptitration schedule according to the ESC guidelines was performed by a cardiologist at the first visit in the HF outpatient clinic. Diuretic regimens and additional therapies (digitalis, anticoagulants, antiarrhythmics) were prescribed as clinical appropriate. In the SOPC group regular home visits by a nurse specialist were arranged after 3,6 and 12 months as well as in case of worsening HF to controll the precribed therapeutic regimen, body weight, heart rate, blood pressure and signs and symptoms of HF.
Results: At time of randomization, neurohumoral status (BNP, N-BNP, N-ANP) and concomitant therapy with RAAS antagonists, additional betablockade, diuretics and digitalis were comparable in both goups. Systolic (146±26 mmHg vs. 127±24 mmHg; $p<0.001$) and diastolic (78±13 mmHg vs. 70±12 mmHg; $p<0.01$) blood pressure was higher in SOPC patients, wheras no difference in heart rate (78±13 beats/minute vs. 70±12 beats/minute) was found. After 1 year follow-up a significant reduction in readmission rate due to worsening HF (13% vs. 33%; $p=0.01$) and a significant reduction in LOS (2,4±9,4 vs. 10,9±22,6; $p<0.01$) was observed in the SOPC group. Additionally, the combined endpoint of readmission due to worsening CHF and/or all cause mortality was significantly lower (17% vs. 33%) in the SOPC group. Conclusion: The use of a HF outpatient clinic in combination with a home nurse specialist is helpful in reducing readmision rate, duration of rehospitalisation and decreasing costs.

MISCELLANEOUS MYOCARDIAL DISEASES

P2403 Alpha-tocopherol attenuates cardiac hypertrophy due to energy metabolic disorder via a non-antioxidant mechanism

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Background: The juvenile visceral steatosis (JVS) mouse is a murine model of systemic carnitine deficiency, which shows disorder of fatty acid oxidation and develops cardiac hypertrophy associated with lipid accumulation. Therefore, the assessment of lipid second messengers including 1,2-diacylglycerol (DAG), an activator of protein kinase C (PKC), may be important to elucidate the pathogenesis of cardiac hypertrophy in this model. Recently, molecular functions of alpha-tocopherol have been reported. Alpha-tocopherol activates DAG kinase and inhibits PKC activity independent of its antioxidant ability. In this study, we investigated the mechanism of cardiac hypertrophy in JVS mice by evaluating the effect of alpha-tocopherol administration.
Methods: Both JVS and control mice were fed a high alpha-tocopherol diet (containing 1000 IU as vitamin E/kg chow) or a standard diet from 4 to 8 weeks of age. Myocardial DAG content was measured by FID-TLC method at 8 weeks of age. Furthermore, its fatty acid composition was analyzed by capillary gas chromatography.
Results: The ventricular to body weight ratio in JVS mice was significantly higher than that in control mice (11.2 vs 3.7 mg/g, $P<0.01$). Cardiac hypertrophy in JVS mice was attenuated by alpha-tocopherol treatment (10.2 mg/g, $P<0.05$). Morphological analysis showed a significantly increased LV wall thickness ($P<0.01$) and myocyte width ($P<0.01$) in JVS mice compared with those in control mice. Alpha-tocopherol treatment also significantly attenuated them. In contrast, alpha-tocopherol treatment had no beneficial effect on cardiac function although echocardiographic analysis revealed lower ventricular fractional shortening in JVS mice than those in control mice ($P<0.01$). The myocardial thiobarbituric acid reactive substance level, an index of oxidative stress, was not affected by alpha-tocopherol treatment. The myocardial DAG level was 2.5-fold higher in JVS mice (2004 ng/ventricular weight vs 806 ng/ventricular weight, $P<0.01$) with a significant increase in fatty acids of 18:1 and 18:2 compared with that in control mice. Alpha-tocopherol treatment reduced the myocardial DAG level in JVS mice (1443 ng/ventricular weight, $P<0.01$ vs JVS mice) without any alteration of fatty acid composition.
Conclusions: These results suggest that alpha-tocopherol partially attenuates cardiac hypertrophy in JVS mice via a non-antioxidant mechanism. An increase in DAG might be involved in the mechanism of cardiac hypertrophy due to energy metabolic disorder.

P2404 Noncompacted ventricular myocardium. Preliminary report of nine cases

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Background: The isolated persistence (i.e., not associated to other congenital abnormalities) of "spongy" ventricular myocardium is a rarely reported and poorly characterized cardiac disorder, due to an incomplete transformation of embryonic trabecular network into adult compact musculature.
Methods: From 1978 to 2001, among 760 consecutive patients (pts) with any heart muscle disease referred to our Institution, 9 (6 males and 3 females, ranging in age from 7 to 48 years) were diagnosed as having isolated noncompaction of the ventricular myocardium (NCVM); 4 cases were familial (2 families). At baseline, pts underwent careful clinical and complete non-invasive and invasive assessment (3 pts refused cardiac catheterisation and myocardial biopsy procedures). All the pts were included in a long-term follow-up program.
Results: Pts had been identified because of the presence of symptoms (dyspnoea n=2, pre-cordial palpitations n=2, complete loss of consciousness n=1), on the basis of EKG abnormalities (n=2), or during family screening for the disease (n=2). At diagnosis (mean time from identification: 63 months, range 1-252) 6, 2 and 1 pts were respectively in NYHA class I/II and III heart failure symptoms. In all the pts, echocardiography demonstrated excessively and grossly prominent trabeculation involving the apical portion of the left (n=3) or both ventricles (n=6), with associated LV dysfunction (mean LVEF 35%, range 17-44). Holter monitoring documented episodes of supraventricular paroxysmal tachycardia in 2 pts and frequent premature ventricular beats in other 2 pts. Long-term medical treatment included ACE-inhibitors (n=6), beta-blockers (n=4), diuretics (n=3), digoxin (n=3), vasodilators (n=1), anticoagulants (n=1), and anti-arrhythmic drugs (n=3). At a mean follow-up of 88.5 months (range 48-144), 7 patients were alive while 1 died for unknown cause 12 years after diagnosis. Among survivors, clinical status was unchanged in 4 cases, worsened in 2 and improved in 1; LV function was unchanged in 3 pts and significantly improved (increase in LVEF>10%) in 2 pts. None of the 7 surviving pts had symptomatic arrhythmias.
Conclusions: Differently from previously published reports, our data on 9 consecutive NCVM pts suggest a favourable long-term outcome, sometimes associated with significant improvement of symptoms and LV function. However, it has to be clarified how the prognosis of the disease depends on the degree of cardiac structural abnormalities, and/or efficacy of heart failure therapies.

P2405 Activities of a national registry of heart tumours

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From 1996 till 2000 we collected 295 heart tumors. The cases were requested annually by a form aproved by the Spanish Society of Cardiology and distributed between the members all around the country (Registro Nacional de Tumores Cardiacos, RNTC). This form contained a questionaire made according to the guidelines of general tumours' registries of Madrid Regional Health Authorities adapted to the heart. It includes case identification, dates of diagnosis and treatment, method of diagnosis, surgical procedures, pathologic examinations and follow up.
Results: 279 pts (126 M/153F. mean age 44.5±25 (range 0-89), 53 were 18 years old or less and 18 were 30 days old or younger) had 295 tumors. Main clinical manifestation were: heart failure (31,1%), arterial embolism (12,9%), arrithmias (9,1%), angina (4%), syncope (3,4%), pericardial tamponade (2,3%), heart block (2%), sudden death (1,8%), asymptomatics (26,1%). Two hundred and sixty were primary heart tumors distributed as follows: myxomas (60,7%), rhabdomyomas (14,2%), angiosarcomas (4,2%), pericardial cysts (3,8%), fibroelastomas (3,4%), linfomas (2,3%), rhabdomyosarcomas (1,9%), leiomyosarcomas (1,5%), hemangiomas (1,5%), mesoteliomas of the AV node (1,1%), malignant histiocytomas (0,7%), teratomas (0,7%), fibromas (0,7%), condrosarcomas (0,7%), lipomas (0,7%), fibrosarcomas (0,3%), myxosarcomas (0,3%), hemagioendoteliomas (0,3%), Purkinje's cells tumours (0,3%). In young cases rhabdomyomas were more frequent in adult cases myxomas. Seven pts had relapsing myxomas, in 4 one time and in 3 two times. Thirty three pts had malignant primitive tumors, (mean age 46,8±22. 16 M/17 F). Left and right atrium were the heart chambers more frequently involved. In malignant cases 20 pts were surgically treated, 2 of them with heart transplantation, 10 received chemotherapy and 6 radiotherapy. Death ocurred in 48 cases. 27 due to tumoral progression, 9 to clinical complications, 9 to other causes not related with the tumour and 3 were undetermined.
Conclusion: The information obtained with the RNTC is useful to put together the experience on these rare heart diseases for epidemiological, clinical and research proposals.

P2406 Herpes simplex virus type 1 infection associated with atrial myxoma

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Background: The etiology of atrial myxoma is unknown, although the constitutional symptoms and laboratory findings suggest an infectious disease. As some histopathological features are similar to Herpes simplex virus type 1 (HSV-1) infections, we hypothesized that HSV-1 may be involved in the pathogenesis of cardiac myxoma.
Methods: Paraffin-embedded tissue samples resected from 17 patients with atrial myxoma were investigated for HSV-1 antigen by immunohistochemistry and virus genomic DNA by nested polymerase chain reaction (nPCR). The histogenesis and oncogenesis of atrial myxoma were assessed by the expression of calretinin, Ki67 and p53 protein respectively and inflammatory infiltrates were characterised by a panel of antibodies against lymphocyte markers. Autopsy samples of cerebrum or myocardium from 5 patients who died of amniotic embolism or enteroviral myocarditis were used for comparison.
Results: HSV-1 antigen was detected in resected atrial myxoma from 12 of 17 patients. Of these 12, eight samples were positive also for HSV-1 genomic DNA: the identity of representative PCR amplicons was confirmed by direct nucleotide sequencing. No HSV-1 antigen or DNA was found in tissue from the comparison group. Most infiltrating lymphoid cells in atrial myxomas were cytotoxic T lymphocytes, although a few T helper cells, natural killer cells and B lymphocytes were present also. Calretinin was found in myxoma cells from all 17 cases but Ki67 was present only in smooth muscle cells or infiltrating cells in some cases. p53 was not detectable in any of the myxomas.
Conclusions: These data suggest that HSV-1 is involved in the pathogenesis of myxoma of neural origin and that atrial myxoma may be a chronic inflammatory lesion of endocardium.

P2407 Cardiac manifestations in patients with primary Sjogren's syndrome

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Objectives: The echocardiographic evaluation of the anatomic and functional heart lesions in patients with primary Sjogren's syndrome (pSS) (without overt heart disease), the comparison of these findings with those of the control group, and the correlation with clinical and laboratory data.
Methods: Seventy eight patients (pts) with pSS (75 women and 3 men, mean age 51 ± 11.6 years and mean disease duration 7.7 ± 4.26 years) and 80 healthy controls (78 women and 2 men, aged 51 ± 9.5 years) were evaluated echocardiographically. Parameters measured included: Left ventricular (LV) dimensions, interventricular septum and posterior wall thickness at end-diastole were measured for the calculation of fractional shortening (FS) and left ventricular mass index with the Penn convention formula. We also evaluated parameters of right ventricular (RV) and LV diastolic function, including early and late atrioventricular (AV) flow velocities (E and A wave respectively), E/A ratio, deceleration time (DT) and isovolumic relaxation time (IVRT). Pulmonary artery systolic pressure (PASP) was estimated by the peak transtricuspid regurgitant velocity jet plus the estimated right atrial pressure, whereas organic valvular involvement was defined as valve thickening and/or regurgitation.
Results: Twenty three (29.5%) pts had mitral valve regurgitation versus 7 controls ($p<0.01$), 6 pts had mild tricuspid regurgitation ($p<0.05$) and 14 (18%) pts had mild aortic valve regurgitation. Pericardial effusion was found in 3 pts whereas fourteen (18%) pts had pulmonary hypertension (PASP > 35 mmHg) ($p<0.001$). Mitral valve regurgitation was significantly associated with the presence of the anti-La antibodies ($p<0.05$) and pulmonary hypertension with lung disease($p<0.05$). The LV mass index of the pts differed significantly from the controls (105.4 ± 14.27 g.m-2 vs 84.71 ± 15.36 g.m-2, $p<0.001$) and was correlated with the presence of purpura ($p=0.02$), lung disease ($p<0.001$), and a positive rheumatoid factor ($p=0.02$). From the indices of LV or RV diastolic function, only the LV IVRT showed significant difference between pts and controls (77.2 ± 4.6 vs 68 ± 5.3 respectively, $p<0.01$).
Conclusion: Patients with pSS and no clinically apparent heart disease had, more often than healthy controls, mild mitral and tricuspid valve regurgitation, and pulmonary hypertension, and had increased left ventricular mass index. The LV mass index is correlated with purpura, lung disease and the presence of rheumatoid factor.

P2408 Left and right atrial remodelling in 153 patients with biopsy-proven cardiac amyloidosis

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Purpose: Cardiac amyloidosis is characterized by extracellular infiltration of myocardial tissue which leads to increased ventricular stiffness. Atrial dilation is expected because of increased filling pressure and amyloid infiltration of atrial wall. However information regarding the frequency and the degree of left and right atrial remodeling in this disease are lacking. Aims of this study were to describe left and right atrial volume and to analyze the variables associatiated with atrial volume increase in a large population of patients with biopsy-proven cardiac amyloidosis. Methods: 153 pts with primary amyloidosis and biopsy-proved cardiac involvement and 26 age and gender matched normal subjects underwent echocardiographic assessment. Left ventricular (LV) septum (ST) and posterior wall (PWT) thickness, diastolic (LVD), systolic (LVS) diameters and ejection fraction (EF) were measured by m-mode echocardiography. E (E) and A (A) waves velocities, E/A ratio and E deceleration time (DTe) were measured. Left atrial volume (LAmax) was measured from biplane apical view (4 and 2 chambers) and the area-length method. Right atrial volume (RAV) was measure from monoplane apical view. Mitral (MR) and tricuspid (TR) regurgitation were semiquantitatively assessed in 4-grades scale. Results: Amyloidosis pts compared with normals have thicker ST (16±3 vs 10±1, p<0.0001), lower EF (47±14 vs 65±7, p<0.0001), shorter DTe (164±44 vs 215±47, p<0.0001) and larger both left (103±3 vs 59±19, p<0.0001) and right atrial volume (96±35 vs 26±6, p<0.0001). In the subgroup of pts with no ST thickness (defined as ST < 13 mm), the difference in term of left atrial volume compare with normals remained highly significant (92±32 vs 59±19 p<0.0001). Determinants of LAmax was ST thickness (r=0.26; p=0.008), LVS (r=0.26; p=0.005), degree of MR (r=0.19; p<0.05), presence of atrial fibrillation (r=0.23; p=0.01) and E/A (r=0.21; p=0.055). Conclusions: Left and right atrial remodeling is a frequent phenomenon in patients with cardiac amyloidosis, even in early phase of the disease. Left atrial volume is mainly related to ventricular remodeling and it might reflect the chronicity and degree of diastolic burden in this unique subset of patients.

P2409 Segmental myocardial wall function by pulsed-wave Doppler tissue imaging in people with human imunodeficiency virus infection

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HIV infected patients (pts) have a longer survival, that may lead to the involvement of organs that are not present in intial phases of this disease, other than the preferential target of this virus, justifying the investigation of its early cardiac manifestations. Pulsed Doppler tissue imaging (DTI) analysis of the left ventricular (LV) myocardial wall velocities during systole and diastole, allows the quantitative evaluation of the segmental (seg) myocardial wall function, preceding its functional LV global dysfunction. The purpose of our study was to investigate early signals of myocardial involvement in HIV infected pts, stage 1 assymptomatic bearers, with no cardiac symptoms and no objective signals of LV global dysfunction (LV fractional shortenning >30% and LV% ejection fraction >50%). With pulsed DTI, we studied a population of 44 HIV 1 and 2 infected young people (Group HIV), mean age 34±11 yrs, 54.6% male gender. Pulsed DTI sample was placed on each one of the 16 LV seg (ASE classification). During 3 consecutive cardiac cycles, we calculated the maximal velocities (Vmax-cm/sec) of the seg pulsed DTI waves, the systolic wave s, early e and late a diastolic waves, and its e/a Vmax diastolic ratio. The pulsed DTI profile was analysed with a Sequoia C256 Acuson equipment, with electronic probes, after B-mode colour Doppler study, sample Doppler 2 mm, and appropriate imaging filters. The results were compared with those of an age matched control group (Group NL) with 15 young healthy volunteers. Both groups were submitted to the same pulsed DTI study protocol. In HIV group, we achieved a greater rate of bifasic s (32% vs 2%; p=0.01) DTI wave profile, a significantly decrease in Vmax s <10 cm/sec (20% vs 3%; p=0.02) seg DTI wave, a significantly decrease in the Vmax e <10 cm/sec (27% vs 3.5%; p=0.01) and a <10 cm/sec (30% vs 4.2%; p=0.01) seg diastolic DTI waves, a greater rate of trifasic (17% vs 1.5%, p=0.03) and quadrifasic (10% vs 0%, p=0.02) seg DTI diastolic waves and a greater rate of Vmax e/a<1 (21% vs 2.5%; p=0.02) seg DTI diastolic wave velocity ratio. Conclusion: In HIV infected patients with no cardiac symptoms and no objective signals of left ventricle global dysfunction, the pulsed DTI was an useful method for segmental quantitative functional analysis. In these HIV pts, we found a remarkable rate of LV seg myocardial dysfunction signals, that suggest the early presence of a certain degree of segmental LV myocardial involvement, despite the initial stage of this viral infection.

P2410 Coronary flow reserve in systemic sclerosis as early marker of cardiac impairment

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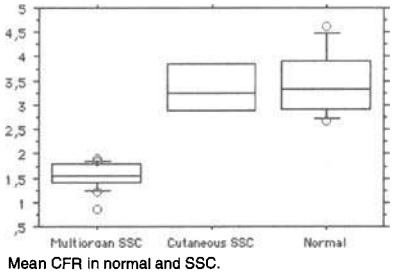
In the last years the advances in medical therapy improved the life expectancy of patients affected by systemic sclerosis (SSC). To the best of our present knowledge, SSC related mortality is frequently associated with cardiovascular impairment and in particular with heart failure. Therefore, we investigated whether the non-invasive determination of coronary flow reserve (CFR) by transthoracic Doppler could be a potential method to detect early dysfunction of cardiovascular system in patients with no apparent cardiac impairment symptoms. 21 patients (19 female, age 49,7± 13,9 years) with an onset of SSC > 2 years, were evaluated. The cardiac evaluation (LVEF, presence of pericardial effusion, EKG rhythm or conduction abnormalities) was normal in all patients whereas cutaneous and visceral involvements was detected in 17 patients and 4 patients showed only cutaneous involvement. The CFR by contrast (Levovist® -300 mg/ml at 1mg/min infusion) enhanced transthoracic second harmonic Doppler was sampled in the left anterior descending coronary artery in SSC patients and in 7 control subjects (normal). CFR was determinated at rest and during hyperemia induced by administration of adenosine at 0,14 mg/kg/min over 5 minutes The CFR was calculated as the ratio of hyperemic to basal peak (VCFR) and mean (MCFR) diastolic flow velocity. We found a reduced CFR (< 2) in the same group of patients with multiorgan involvement and normal CFR (> 2) in the remaining SSC 4 patients and in the normal group. CFR impairment could relate to an earlier coronary microvascular dysfunction and seems to be an effective, noninvasive tool to assess cardiac involvement in SSC. Further evaluation could be performed to assess the prognostic value of these findings.



Mean CFR in normal and SSC.

P2411 Cardiac involvement in systemic lupus erythematodes – visualization with contrast enhanced cardiac magnetic resonance imaging

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Background: Systemic lupus erythematodes (sLE) is a systemic rheumatic disease involving different organs. Cardiac manifestation is more commonly found at autopsy than clinically. Myocarditis is clinically found in up to 10% of patients, whereas the incidence in autopsy studies is about 40%. On the other hand for the guiding of new therapeutic strategies the diagnosis is essential. Contrast enhanced Magnetic resonance imaging was shown to be sufficient in detecting myocardial injury due to different causes.

Patients and Method: We applied contrast-enhanced MRI in 18 patients with proven sLE. 10 patients suffered from stable disease (sLE), whereas 8 patients suffered from acute disease as defined by the ECLAM-activity-score and ANA-values (sLE acute). We performed standard T1-weighted multislice spin-echo sequences (TE 30ms; TR 480-725 ms; slice thickness 6 mm) in an axial and short-axis orientation (before and after application of 0.1 mmol/kg Gd-DTPA (Magnevist®, Schering AG; Berlin, Germany) on conventional MRI systems (1.0 T; Siemens-Expert; Siemens AG, Erlangen, Germany and 1.5 TSigna CV/i; GE; Milwaukee, USA, respectively) using a body coil. The relative global signal enhancement (RE) of the myocardium as related to the skeletal muscle was calculated. Furthermore, we compared the left ventricular ejection fraction (LVEF) as determined by gradient echo sequences. Results ot both patient groups were compared with 10 healthy volunteers (vol).

Results: The RE of patients with acute sLE (5.5±0.9) was significantly higher than that of the other patients with sLE (3.0±0.4; p<0,004). The RE of the volunteers (2.0±0.3) was significant lower as compared to that of acute sLE (p<0,0001), and there was also no significant difference to the group with the stable sLE-patients. There was no significant difference of the LVEF between any of the groups (vol: 70±2%; sLE:69±4%; sLE acute 68±3%; p=n.s.). Furthermore, in all patients with acute sLE, a subendocardial pronouncement of the enhancement was evident, whereas this pattern was present in only 50% of the other sLE patients and never detectable in vol.

Discussion: In patients with normal LVEF, the acute myocardial injury in patients with SLE is detectable by ceMRI. The impact of the subendocardially pronounced signal enhancement for the degree of the disease is not yet clarified.

Conclusion: Contrast enhanced MRI is helpful in detection of myocardial involment in patients with systemic lupus erythematodes.

P2412 Cardiac dimensions in junior elite athletes

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Background: Regular intense physical exercise can cause cardiac adaptations reflected by increased left ventricular cavity size raising the differentiation from cardiomyopathy. Unlike senior athletes, there is a paucity of data regarding cardiac dimensions in junior elite athletes. This is particular relevance as death due to cardiomyopathy is most prevalent in this age group.
Methods: Between 1996 and 2000, 1610 asymptomatic junior elite athletes (74% male) in the United Kingdom were evaluated using 2-D echocardiography. The athletes (age 15.6 ± 1.4 years; range 14-18 years inclusive; body surface area (BSA) 1.74 ± 0.16 m^2; range 1.09-2.23 m^2) were from a variety of sporting disciplines including endurance, team and technical sports (tennis 26%, football 24%, swimming 12%, rugby 9%, rowing 8%, cycling 8%, triathlon 5%, other 8%). In addition, 368 healthy non-athletic controls matched for age, gender and BSA were evaluated.
Results: Both groups were matched for age (15.5 ± 1.6 v 15.2 ± 1.2 years; p = 0.1) and BSA (1.74 ± 0.2 v 1.73 ± 0.4; p = 0.2). Athletes had a greater left ventricular end-diastolic diameter (LVEDD) than the control group (50.8 ± 3.2 v 47.9 ± 3.5 mm; p < 0.0001). The LVEDD correlated with BSA (r = 0.6, p > 0.0001) and was greater in males despite correction for BSA (51.6 ± 3.3 v 47.7 ± 3.3; p > 0.001). The left atrial size was also greater in athletes (33 ± 3.5 v 31 ± 5 mm; p = 0.0002). Systolic function (fractional shortening 33.1 ± 3.5 v 31.9 ± 3.9; p = 0.4) and E/A ratio (2.25 ± 0.7 v 2.14 ± 0.2; p = 0.3) was similar in the two groups.
33% of athletes had a LVEDD exceeding predicted upper limits of normal. The LVEDD in this group was 54.4 ± 2.1 mm (range 52-60mm). The fractional shortening in this group was normal (38 ± 3%; range 32-43%). No female athlete had a LVEDD > 55mm and no male athlete had a LVEDD > 60mm.
Conclusion: (1) The increase in cavity dimension seen in junior athletes is modest (2.9mm; 6%) and less than that reported in studies of senior athletes. This may reflect shorter cumulative duration of training. (2) Left ventricular dilatation in athletes occurs in the context of normal systolic function differentiating it from dilated cardiomyopathy. A LVEDD > 60mm suggests pathological dilatation rather than physiological adaptation. (3) The LA is dilated in athletes but in proportion to LVEDD reflecting a generalised increase in preload with exercise rather than elevated end-diastolic pressures and diastolic abnormalities.

P2413 QTc-interval dispersion is not associated with mortality in patients with heart failure due to Chagas' cardiomyopathy

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QTc-interval dispersion (QTc-d) has been considered a marker of mortality for patients with nonchagasic heart failure. QTc-d is increased in patients with heart failure due to Chagas' cardiomyopathy as compared with controls. Nevertheless, the value of QTc-d to predict mortality in patients with heart failure due to Chagas' cardiomyopathy is unknown. Accordingly, this study aimed at assessing the association of QTc-d with mortality in patients with heart failure due to Chagas' cardiomyopathy.
From january, 2000 to june, 2001, 63 consecutive patients followed at the Heart Failure Outpatient Service with a positive serologic test for Chagas' disease were considered for the study. All chagasic patients underwent history-taking, physical examination on admission, 12-lead resting ECG, X-Ray chest, serological tests and dopplerechocardiography. Patients were diagnosed as having heart failure due to Chagas' cardiomyopathy on the basis of cardiomegaly on X-Ray chest or decreased left ventricular ejection fraction on dopplerechocardiography. Twenty-two patients wearing artificial pacemakers and 11 patients with atrial fibrillation were ruled out, whereas the remaining 30 patients were entered the study. The QTc interval was measured in at least 5 leads. QTc-d was defined as the difference between maximum and minimum QTc. Fifteen patients with no previous cardiac history served as controls.
Eleven (37%) of 30 patients with heart failure due to Chagas' cardiomyopathy died during the study period. Mean left ventricular ejection fraction was 32±13% in survivors and 30±13% in nonsurvivors chagasic patients (p>0.05). QTc-d was 40.6±10.94 msec in controls, 98.75±37.13 msec in survivors and 117.59±37.91 msec in nonsurvivors chagasic patients (p<0.0001 by Kruskal-Wallis test). No difference was observed between survivors and nonsurvivors chagasic patients with regard to mean QTc-d values.
Thus, QTc-d seems not to be associated with total mortality in patients with moderate to severe heart failure due to Chagas' cardiomyopathy.®

P2414 Microangiopathy as diagnostic and prognostic marker in cardiac sarcoidosis

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Background: Microangiopathy presenting as basal lamina layering (BLL) around the microvasculature detected by electron microscopy is often observed in various tissues affected by sarcoidosis, including the heart. The clinical significance of microangiopathy is unknown, however in relation to cardiac sarcoidosis. Methods: To clarify the diagnostic and prognostic significance of microangiopathy, we analyzed the clinicopathological findings and outcomes in 15 cases of CS in which sarcoidosis in the lung, skin, lymphnode, or heart was confirmed histologically, and in which ultrastructural observations of heart biopsy specimens were made. Electron microscopy findings in 25 cases of idiopathic dilated cardiomyopathy (IDC) were used for comparison. Results: Granulomas were confirmed in only 3 patients (20%) by heart biopsy. The incidence of BLL was significantly greater in cases of CS than in cases of IDC (12/15:73% vs. 7/25:28%, p<0.05). The presence of BLL >4 layers showed a sensitivity of 60%, a specificity of 92%, and a predictive accuracy of 78% for differential diagnosis of CS and IDC. Left ventricular (LV) ejection fraction (39±13% vs. 59±23%, p<0.05) and % area of interstitial fibrosis (16±8 vs. 8±4, p<0.05) in 9 patients with BLL >4 layers (group A) was significantly lower than that in the other 6 patients (group B). A cardiac event (worsening heart failure requiring hospitalization, sustained ventricular tachycardia, or cardiac death) occurred in 6 group A patients (67%) and 1 group B patient (17%) during the mean follow-up period of 54 months (p<0.05), and 5 group A patients (56%) died. Despite corticosteroid treatment, group A patients showed a significant increase in LV volume index (78±21ml/m^2 to 103±23ml/m^2, p<0.01) and thinning of the interventricular septum (12±4mm to 9±3mm, p<0.01). No group B patient died, and echocardiographic parameters were unchanged in this group. Conclusions: BLL is a useful diagnostic marker of CS. Microangiopathy may be related to ventricular remodeling, disease progression, and poor clinical outcome in cases of CS.

VALVE DISEASE – MISCELLANEOUS

P2415 Alterations in myocardial creatine kinase may be used to detect myocardial maladaptation in chronic valvar heart disease

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Background: The creatine kinase (CK) system (creatine-phospat + ADP = creatine + ATP) is the primary energy providing system of the heart. To maintain increased myocardial workload an upregulation of the CK activity, which results in fastened ATP resyntheses, is necessary to meet the elevated energy demand. It is still controversial whether CK activity is decreased in patients with cardiac failure. The isoenzyme CK-MB has a higher affinity to ADP and in case of a reduced amount of phosphocreatine ATP produces more efficiently than CK-MM. A shift of the isoenzyme pattern from CK-MM to CK-MB is regarded as a mechanism of myocardial adaptation. We analyzed whether changes of the CK system can be used as a biochemical marker to determine myocardial maladaptation to volume and/or pressure overload in valvar heart disease (VHD).
Methods: In right ventricular biopsies from 12 patients (P) with aortic stenosis (pressure loss (PL) 0.2-2.9 mmHg/ml stroke volume, cardiac index (CI) 2.0-4.4 ml/min/m^2, wall stress (WS) 85-174 g/cm^2) and from 12 P with valvar regurgitation (aortic[AR] n=6, mitral[MR], n=6) (regurgitation fraction (RF) 22-55%, CI 1.8-4.5 ml/min/m^2, WS 75-164 g/cm^2), total CK activity was measured by disappearance of NADP at 450 nm and CK isoenzyme pattern by gel electrophoresis. As controls, endomyocardium from explanted organs with terminal heart failure (EXPL,n=7), from P with dilated cardiomyopathy (DCM,n=12) and from 6 healthy hearts (C) were examined.
Results: In comparison to C (47.2±5.2 U/mg protein) mean CK activity was reduced in P with pressure overload (AS: 41.9+13.6 U/mg), volume overload (AR/MR: 38.4±17), in EXPL (43.3+16.2) and significantly in P with DCM (20.1±9.9)(p<0.05). In VHD, CK activity increased parallel to the severity of diastolic (LVEDP, r=0.42) and decreased parallel to systolic dysfunction (CI, r=-0.22). In DCM, CK activity decreased parallel to systolic (CI, r=0.40)and diastolic (LVEDP, r=0.24) dysfunction. There was no correlation between CK activity and DV or RF. An CK isoenzyme shift was found in P with VDH parallel to an elevation of WS (CK-MB/CK-MM vs WS, r=0.41).
Conclusion: A decrease of myocardial CK activity and an isoenzyme shift from CK-MM to CK-MB indicates myocardial maladaptation in VHD.

P2416 Coagulations, fibrinolytic system activation and endothelial dysfunction in patients with mitral stenosis in sinus rhythm

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SUMMARY Background. Systemic embolism is an important complication in patients with mitral stenosis. Anticoagulation treatment can prevent this serious complication in patients with mitral stenosis in atrial fibrillation, but in sinus rhythm the place of this treatment is in argument. In this study, our aim is to determine the hemostatic parameters of mitral stenotic patients in sinus rhythm and also to compare the systemic hemostatic parameters of patients both in atrial fibrillation with LASEC (left atrium spontaneous echo contrast) and without LASEC and normal population.

Methods: 46 patients with mitral stenosis contributed to this study. 28 patients were in sinus rhythm and 18 patients were in atrial fibrillation. None of the patients had left atrial trombus in transesophageal echocardiography. We studied systemic venous fibrinogen, D-dimer, antitrombin-III, tissue plasminogen activator, plasminogen activator inhibitor-I, von Willebrand factor, platelet factor 4 in these patients. The patients were divided into subgroups, first according to their rhythm as sinus and atrial fibrillation than those with LASEC and sinus rhythm, those with LASEC and atrial fibrillation, those without LASEC and sinus rhythm, those without LASEC and atrial fibrillation. All of these groups were compared with control group.

Results: Our results suggest that fibrinogen, D-dimer, antitrombin-III, von Willebrand factor, platelet factor 4 levels were greater in sinus rhythm and atrial fibrillation groups than the control group. This was significant statistically ($p<0.05$). Also in presence of LASEC both in sinus rhythm and atrial fibrillation fibrinogen, D-dimer, antitrombin-III, von willebrand factor and platelet factor 4 levels were significantly higher compare to control group ($p< 0.05$). Without LASEC fibrinogen, antitrombin-III, von Willebrand levels were high only in atrial fibrillation group ($p<0.05$). D- dimer, platelet factor 4 were greater in atrial fibrillation and sinus rhythm than controls ($p<0.01$). These parameters were also high in atrial fibrillation than sinus rhythm ($p<0.05$). We studied also tissue plasminogen activator and plasminogen activator inhibitor-I levels. Only tissue plasminogen activator levels were higher in atrial fibrillation group than sinus rhythm and control group ($p<0.05$).

Conclusions: In patients with mitral stenosis but in sinus rhythm, especially the patients with LASEC, coagulation activation, platelet activation and endothelial dysfunction are similar in patients with atrial fibrillation.

P2417 Should we still anticoagulate patients with atrial fibrillation and/or mitral stenosis in presence of severe mitral regurgitation?

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The risk of left atrial thrombus (LAT) formation and/or systemic embolism (SE) have been documented to be high in pts with atrial fibrillation (AF) and/or mitral stenosis (MS),and to be low in pts with severe mitral regurgitation (MR). However, indications of anticoagulation in pts with severe MR concommitant with AF and/or MS does not consider any beneficial impact of MR on thromboembolic risk. We aimed to investigate the incidence of LAT and history of SE in patients who underwent mitral valve surgery,and to assess whether severe MR prevents LAT and SE in pts with chronic AF.The study population comprised 979 pts(F 636,M 343,age 40±14.5) in whom valve surgery was performed because of pure or predominant MS(n=517),severe MR(n=388),and MS concomitant with severe MR (n= 74).Preoperative rhythm was AF in 530 pts, and sinus rhythm (SR) in the remainder. History of SE before surgery was documented in 146 pts with MS, but in none of them with severe MR with or without MS. Anticoagulation was noted in 166 pts with history of SE and/or LAT diagnosed by echo. Age, sex, and left atrial diameter were not different between three groups ($p>0.05$). Intraoperative assessment disclosed LAT in 108 pts. In MS group, pts with AF had a higher incidence of LAT as compared to pts with SR (31.3% vs 4.8%,$p<0.001$). However, none of pts with severe MR had LAT,and LAT within the appendage was detected in one pt with MS+MR with AF. Incidence of LAT was lower in MR group regardless of rhythm as compared to pts either with MS concommitant with AF ($p<0.001$) or SR ($p<0.05$). Similarly, pts with MS+MR had a lower incidence of LAT than pts with MS and AF ($p<0.001$), and pts with MS and SR ($p<0.05$).

We conclude that incidence of LAT and/or SE are the highest in MS with AF, and even high in MS with SR whereas pts with severe MR carry the lowest risk regardless of rhythm and MS. Severe MR seems to prevent LAT and SE in chronic AF even in the absence of anticoagulation. In patients with severe MR indications of anticoagulation for AF and MS may need to be reevaluated.

P2418 The relationship between tumor markers and echocardiographic findings in carcinoid heart disease

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Background: Carcinoids are neuroendocrine tumours that secrete active substances which could cause carcinoid syndrome (CS) and carcinoid heart disease (CHD). Pathogenesis of CHD is not completely understood. AIM: To explore differences in biochemical markers (urine levels of 5-HIAA and serum levels of chromogranin A and TGF-beta1) between two groups of patients with CS (group A with CHD and group B without CHD) through which we wanted to gain more insight in the pathogenesis of CHD and confirm the diagnostic value of biochemical markers for CHD. METHODS: The prospective study included 12 pts who were at the time of study diagnosed and treated for CS. Group A included 5 pts and group B 7 pts. All pts but 1 had already started with octreotid treatment before our echocardiographic analysis were made. 5-HIAA (mg/24h urine), chromogranin A (μg/l) and TGF-beta1 (μg/l) were measured for each patient at the time of echocardiographic analysis (control measures); pre-treatment measures of 5-HIAA before treatment with octreotide were also obtained. RESULTS: The two groups did not differ in duration of symptoms of CS (53 vs. 50 months). The most common echocardiographic findings in group A were morphologic changes of the tricuspid valve with tricuspid regurgitation. Group A had significantly higher concentrations of chromogranin A (median 216 vs. 36; $p<0.05$). The correlations between levels of chromogranin A and 5-HIAA were statistically significant both for the time before (Kendall Tau= 0.49; $p<0.05$) treatment with octreotide and for the time when echocardiographic analysis were made (Kendall Tau= 0.69; $p<0.01$). Only control (median 600 vs. 70) but not the pre-treatment measures (median 219 vs. 33) of 5-HIAA between two groups were statistically significant ($p<0.01$). Decrease of 5-HIAA levels after treatment with octreotide was insignificant. The two groups did not differ in serum levels of TGF-beta1 (median 23.5 vs. 39.4). CONCLUSIONS: Appearance of CHD is not dependent on the duration of symptoms of CS. Chromogranin A and 5-HIAA are useful in diagnostics and follow-up for patients with carcinoid syndrome and carcinoid heart disease. The levels of 5-HIAA in our study confirm the important role of serotonin in pathogenesis of CHD. Treatment with octreotide does not cause a significant fall in the 5-HIAA concentrations and apparently has no impact on development of CHD. Serum concentrations of TGF-beta1 were not found to be helpful in diagnostics of CS or CHD.

P2419 Outcome of percutaneous mitral baloon valvuloplasty: comparison of the inoue and retrograde non-transseptal techniques, from a single center

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Introduction: The transseptal Inoue (IN) and to a lesser extend retrograde non-transseptal (RNT) techniques are established procedures for percutaneous mitral balloon valvuloplasty (PBMV) in patients with mitral stenosis. However, a head to head comparison of these two techniques, especially from a single center, has not been reported yet.

Methods: 72 consecutive patients (IN:35 and RNT: 37) underwent PMBV in our clinic from October 1993 to December 1999. All baseline and procedural characteristics were compared, as well as the immediate and long-term (42 ± 12 months) outcome of the pts.

Results: Baseline characteristics were similar in the two groups. Immediately after the PMBV, mitral valve area (MVA) increased from 1.04 ± 0.16 to 1.6 ± 0.3 in group A and from 1.06 ± 0.23 to 1.55 ± 0.3 in group B. There was a higher percentage of mild mitral regurgitation (MR) after the RNT technique, compared with the IN ($p=0.034$). A successful immediate result was achieved in 91% of patients in IN and 89% of patients in RNT group. Mean fluoroscopy time was 31 ± 16.1 in IN and 39 ± 11 min in RNT ($p=0.024$). There were no procedural deaths in either group. After discharge, major adverse cardiac events (MACE: mitral valve replacement, repeat BMV) occurred in 3 (8%) pts in IN and 5 (13.5%) patients in RNT group (NS). There were no deaths at follow-up. Follow-up echocardiographic assessment of MVA revealed no significant change.

Conclusions: The IN and RNT techniques are comparable regarding the achieved MVA with slightly more frequent MR post-RNT PBMV. The IN requires significantly less fluoroscopy time. MACE and event free survival rates at follow-up were similar in the two groups.

P2420 Prevalence of rheumatic heart disease among schoolchildren in urban areas of Hamedan province, situated in the west of Iran

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Background and Objectives: Rheumatic heart disease(RHD), the most important cardiovascular disease, continues to be a common health problem in the developing world, causing morbidity and mortality among both children and adults. There are only a few population surveys available in Iran to determine the prevalence of RHD. This survey was undertaken to estimate its prevalence among schoolchildren in urban areas of Hamedan province, situated in the west of Iran.
Material and Methods: The study was a cross sectional survey, carried out by a specially trained medical team headed by a cardiologist. The study involved all of the schoolchildren (7-18 years of age) from 7 city of Hamedan province in 1992. Diagnosis of rheumatic heart disease was confirmed only after Doppler echocardiography in suspected cases.
Results: A total of 167,786 children on the school register (104,242 boys and 63,544 girls) were examined generally and specifically for evidence of RHD. Out of the 167,786 children screened, 714 were suspected cases and 23 were confirmed cases of RHD (14 boys and 9 girls), giving an overall prevalence rate of 1.37 per 10000 children with no significant difference among the age groups of 7-11, 12-14 and 15-18 years. Only sixteen of the 23 patients were aware of their disease (69.6%). The mitral valve was affected in all of the cases. Out of 23 cases of RHD, isolated mitral regurgitation(MR) was present in six (26%), combined MR and mitral stenosis (MS) in nine (39.1%), combined MS and aortic insufficiency(AI) in one, and combined MR and MS and AI in four patients (17.3%). Also one patient had acute rheumatic carditis. The tricuspid valve and pulmonary valve involvement were not seen in any cases.
Conclusion: This study revealed a lower prevelance of RHD than that, reported in most earlier studies from developing countries. The lack of patient's awareness about their disease, noted among the patients revealed that public health education is necessary. Also, regular surveys are needed to identify new cases and to ensure secondary prophylaxis; thereby preventing the progression and the severity of the valvular lesion.

P2421 Herpes simplex virus type 1 infection in rheumatic heart disease

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Background: Rheumatic heart disease (RHD) is the most important sequela of rheumatic fever: evidence that streptococcal infection is the etiological agent is strong, but indirect. Herpes simplex virus type 1 (HSV-1) can establish latent infection in autonomic ganglia innervating cardiac valves and virus reactivation produces mucocutaneous lesions within the distribution of the affected nerve. We hypothesized that reactivation of HSV-1 in autonomic nerves, by infection, stress or trauma, may involve cardiac valves and contribute to the onset and development of rheumatic valvular disease.
Materials and Methods: Formalin-fixed, paraffin-embedded valvular samples from 17 patients diagnosed clinically and histologically with RHD were investigated for HSV-1 infection. HSV-1 antigen in tissue was detected by immunohistochemistry with an HSV-1-specific monoclonal antibody and the EnVision detection system (DAKO). Part of the glycoprotein D gene sequence of HSV-1 was amplified by nested PCR using HSV-1 specific primers. PCR products were characterized by agarose gel electrophoresis and direct nucleotide sequencing. b-globin gene sequences were amplified from each sample at the same time, as reagent control. Valvular tissues collected at autopsy from 5 cases of sudden death without myocardial or valvular lesions served as a comparison group. HSV-1-infected lung tissue was used as positive control.
Results: HSV-1 antigen was detected in valvular tissues from 14 of 17 patients. Five of these 14, but no antigen-negative sample, were positive also for HSV genomic DNA. Nucleotide sequence of nPCR-amplified HSV DNA, determined by automated cycle sequencing in both orientations, was homologous with the HSV-1 glycoprotein D gene. HSV-1 antigen was present also in one case of sudden death but HSV-1 DNA was not found in tissue from any case in the comparison group. Results from reagent and positive controls were as anticipated.
Conclusions: This is the first study to show the presence of HSV-1 antigen and genomic DNA in valvular tissues, supporting the concept of HSV-1 involvement in rheumatic valvular disease. HSV-1 infection may damage valves directly or act with additional etiological factors such as prior streptococcal pharyngitis, leading to initial and recurrent episodes of rheumatic heart disease.

P2422 Long-term prognosis of infective endocarditis. Are embolic phenomena associated with a higher mortality?

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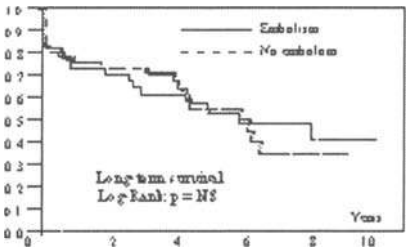
Infective endocarditis (IE) may be complicated with embolic phenomena (EP). However, it is not clear if EP imply itlself higher mortality in these patients. Aim of the study was to elucidate whether EP in IE are associated with higher long-term mortality.
We studied and followed-up for a mean of 3.1 years (range 0.5-15) 150 patients with IE. Of them, 65 (43%) had any EP at clinical presentation or during hospitalization.
Patients with EP were younger (46±18 vs. 55±18 yr, $p<0.01$) and more often drug abusers (38% vs. 19%, p=0.02), and had less frequency of heart failure (29% vs. 50%, $p<0.01$), S. aureus as etiological agent (44% vs. 23%, p=0.02), and mitral involvement (35% vs. 21%, $p<0.05$).



Long-term outcome.

Prognosis of patients with vs without EP

		Embolisms	No embolism	p
During hospitalization	Mortality	19%	15%	NS
	Surgery	36%	53%	0.03
1-year	Mortality	21%	26%	NS
	Surgery	39%	58%	0.01
5-year	Mortality	43%	45%	NS
	Surgery	49%	62%	0.01

Thus, EP are not associated with higher mortality neither during hospitalization nor at long-term.

Day 4

Tuesday 3 September 2002

FAMILIAL ARRHYTHMIAS: THE DOOR TO THE GENETIC BASIS OF SUDDEN DEATH

2515 Genotype/phenotype correlation in catecholaminergic ventricular tachycardia: evidence for heterogeneous clinical presentation

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We recently demonstrated that mutations in the cardiac ryanodine receptor gene (RyR2) cause an inherited form of cardiac arrhythmia and sudden death, called catecholaminergic polymorphic ventricular tachycardia (CPVT). CPVT is inherited as an autosomal dominant trait and its phenotype is characterized by polymorphic ventricular tachycardia triggered by physical activity or emotional stress. RyR2-mutations most likely cause a "gain of function" leading to intracellular calcium overload predisposing to the development of delayed afterdepolarization-mediated triggered arrhythmias. Here, we report the first assessment of genotype-phenotype correlations in patients with (RyR2-CPVT) and without (nonRyR2-CPVT) mutations on the RyR2 gene. Thirty probands (PB) and of 118 family members (FM) were evaluated and molecular screening of the RyR2 gene was performed. The clinical evaluation of PB showed a heterogeneous morphology of the ventricular tachycardia (VT): 14/30 bidirectional VT(bVT), 12/30 polymorphic VT (pVT) and 4/30 catecholaminergic idiopathic ventricular fibrillation (cIVF). RyR2 mutations were identified in 14/30 PB and in 9 FM (4 silent mutation carriers). All the mutations identified involved highly conserved and functionally relevant regions of the RyR2 channel. When CPVT patients with and without mutations in the RyR2 gene are compared it is shown that no difference is present in the distribution of the VT morphologies and in the history of sudden cardiac death among family members (37% and 31% in RyR2-CPVT and in non RyR2-CPVT families respectively). Interestingly however RyR2-CPVT patients develop events at younger age than non RyR2-CPVT (8±2 vs. 20±12 years; $p < 0.004$). Among RyR2-CPVT patients, male gender is a strong risk factor for syncope (Relative Risk 4.2). Based on these data, that represent the first genotype-phenotype correlation study in CPVT on the largest reported series of patients it may be concluded that: 1) The morphology of ventricular tachycardia in CPVT may be either bi-directional or polymorphic. 2) A defect in the RyR2 gene is the underlying substrate of adrenergically-mediated idiopathic ventricular fibrillation. 3) RyR2 mutations account for approximately 45% of all cases of CPVT. 4) RyR2 mutation carriers present cardiac events at younger age and male gender is a risk factor for the development of cardiac arrhythmias.

2516 Codon 218 within the KCNJ2 gene is a hot-spot for mutation in Andersen Syndrome

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Introduction: Andersen syndrome (AS) is characterised by the triad: cardiac arrhythmias, periodic paralysis (PP) and dysmorphic features. It has recently been associated with mutations in the KCNJ2 gene that encodes the inward rectifying potassium channel Kir2.1. In this study: 1) we carried out mutational analysis in KCNJ2 in 2 families with features of AS. The families had predominantly the cardiac phenotype and mild dysmorphic features. Neither family had PP. 2) We tested the possibility that mutation in KCNJ2 could form the basis of prolonged QT in patients (n = 18) presenting solely with prolonged QT-interval (in the absence of PP and dysmorphic features; i.e. congenital Long QT syndrome patients; cLQTS), in whom mutation in the known cLQTS genes (KCNQ1, KCNH2, KCNE1, KCNE2, SCN5A) has been excluded.
Methods: Mutational analysis was carried out on the entire coding region of the gene by sequencing of PCR-amplified fragments.
Results: 1) Two different mutations, both within codon 218 were identified in the two families with features of AS: a CGG->TGG and a CGG->CCG, leading to the substitution of Arg 218 into Trp and Pro respectively. The mutations segregated with features of the disorder in the two families. 2) No mutations were identified within the cohort of cLQTS patients.
Conclusions: 1) Besides the two families presented herein, mutation at codon 218 within KCNJ2 has been reported in two other families with AS. One of these reported mutations results in the same nucleotide substitution (CGG->TGG; resulting in R218W) as in one of our families. Taken together, it appears that this codon represents a hot-spot for mutation. This could relate, at least in part, to the fact that this codon contains a CpG motif, a known hot-spot for mutation. Furthermore, the fact that the two families presented here displayed predominantly the cardiac phenotype together with mild dysmorphic features and no PP, underscores the variable expressivity of the disorder. 2) However, the fact that no mutations were identified in the cLQTS cohort implies that mutation in KCNJ2 does not form the basis for QT-prolongation in patients presenting solely with prolonged QT-interval, i.e. in the absence of PP and dysmorphic features.

2517 Female predominance and increased maternal transmission in genotyped families affected by long-QT Syndrome

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Introduction: Female predominance has repeatedly been observed in long-QT syndrome (LQTS) which is apparently not in accordance with Mendelian transmission of an autosomal dominant character. We thus analyzed the segregation of paternally versus maternally inherited LQTS mutations in order to state whether a disequilibrium could explain the female predominance.
Methods: 97 French LQTS families recruited by a single index case were found to carry mutations in KCNQ1 or KCNH2 (LQT1: n=64; LQT2: n=33). Analysis was performed only on genotypically ascertained individuals with genotyped ascendants and/or descendants, as well as completely genotyped sibships (n=488 for LQT1 and n=186 for LQT2). Single ascertainment correction of the proband family nucleus was done according to Li (1961).
Results: Sex ratio analysis: The female predominance among the probands was marked (67%, for LQT1, n=43 and 66% for LQT2, n=22), while it was less evident, after single ascertainement correction, among the genotyped subpopulations presenting 58% of female mutation carriers for LQT1 and 56% for LQT2.
Transmission analysis: Analysis of the maternal versus paternal inheritance of the mutation revealed a higher incidence of maternal transmission (61% for LQT1, n=64, 59% for LQT2, n=37) than paternal one. We examined in more detail the segregation and sex ratio of the offspring of LQT1 and LQT2 carriers and noted a pronounced segregation disequilibrium in the offspring (n=115) of female LQT1 carriers. Indeed, the distribution of the offspring was the following: 41 affected females, 23 unaffected females, 27 affected males and 24 unaffected males, showing a significant excess of affected female offspring (60,3% affected females vs 39.7% affected males, $p < 0, 05$). In constrast, the offspring (n=88) of male LQT1 carriers showed a cassical Mendelian distribution. Due to the small number of LQT2 carriers(n=23), more data need to be collected to conclude for this subgroup.
Conclusions: We confirmed a female predominance not only among probands, but also among proband-independent LQT1 and LQT2 carriers. A segregation disequilibrium in the transmission pattern of LQT1 mutations was found and clearly revealed a tendency for female LQT1 carriers to transmit the deficient trait more often to the female than male offspring. The physiological mechanism underlying such a selection of female versus male is yet unknown.
Reference: Li CC. 1961. Human Genetics: Principles and Methods. Eds: MacGraw-Hille Book Company Inc., New York. pp 58 - 79.

2518 Complete sequencing of Ryanodine Receptor 2 gene in isolated cases affected with effort-induced polymorphic arrhythmias

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Effort-induced polymorphic ventricular arrhythmias (PVA) consist of left and right bundle branch block morphology and different axis deviation, which appear in response to vigorous exercise. Coupling interval of first premature beats is never short.
Ryanodine receptor gene type 2 (RYR2) mutations have been associated to this arrhythmias, which occur either in subjects with apparently normal heart or in patients affected with arrhythmogenic right ventricular cardiomyopathy type 2 (ARVD2).
We detected 7 different RYR2 mutations in 10 apparently unrelated subjects affected with PVA (in three instances, the same mutation was found in two patients). In 9 cases, the mutation was detected in additional family members, thereby confirming familial inheritance; in one case, familiarity could not be assessed due to the small size of the family.
In additional 3 subjects affected with PVA, considered to be isolated cases due to the lack of affected relatives, the complete sequencing of the RYR2 gene was performed. All the 105 exons were PCR amplified from genomic DNA and directly sequenced in both strands. Although several single-nucleotide polymorphisms (SNPs) were observed, no mutations were identified. The negative results obtained in these 3 isolated cases support the hypothesis of heterogeneity of PVAs.

2519 Overexpression of A1 and A3 adenosine receptors causes bradycardia and atrioventricular nodal conduction delay-a molecular model for sinus node dysfunction?

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The molecular causes of sinus node dysfunction and the often associated AV nodal conduction disturbances are not well understood. Acute administration of adenosine suppresses AV nodal conduction and affects sinus node function. We studied whether a chronically enhanced response to adenosine changes sinus nodal and AV nodal function.

Three months old mice with cardiac-specific overexpression of A1 adenosine receptor (A1AR+) and mice with high-level cardiac-specific overexpression of A3 adenosine receptor (A3AR+) and their wild-type littermates (WT) were instrumented with a telemetric Holter ECG system. The ECG was continuously analyzed during defined periods of normal activity, during a standardized exercise protocol (4 minutes swimming), and 1 hour after exercise. Pertussis toxin (PTx, 150microg/kg body weight, n=4 A1AR+, 3 WT) was injected intraperitonally to block the Gi-adenosine signaling pathway. Atrial size was measured by biplane echocardiography.

A1AR+ mice (n=7) had lower mean heart rates during exercise (580±47 vs 698±84*, all values given in beats/min as mean±SD, * indicates $p<0.05$), and 1h after exercise (495±38 vs 592±61*). During normal activity, mean heart rate was not significantly different (414±47 vs 455±60), but the difference between the lowest and highest heart rate was smaller in A1AR+ mice (38±9 vs 123±64*). Maximal heart rate was lower in A1AR+ mice during all protocol parts (normal activity: 496±40 vs 522±55*, exercise: 640±37 vs 768±73*, 1hr after exercise: 638±45 vs 798±57*). Minimal heart rate was not different during normal activity (361±64 vs 405±75), 1hr after exercise (422±37 vs 455±63), or during exercise (515±43 vs 540±115). PTx reversed bradycardia in AR1+ mice after 36-48 hrs. Atrial size was not different between A1AR+ and WT hearts.

A3AR+ mice (n=3) also had lower mean heart rates during normal activity (393±100 vs 517±55*), exercise (539 ±50 vs 756±28*), and 1h after exercise (470±75 vs 671±61*). Maximal and minimal heart rates were lower in A3AR+ mice during all protocol parts (normal activity: Max 438±35 vs 558±41*, min 360±135 vs 449 ±49*, exercise: Max 654±39 vs 853±114*, min 231±34 vs 459±57*, 1hr after exercise: Max 667±15 vs 834±31*, min 381±68 vs 623±80*). In A3AR+ mice, PQ interval was dramatically increased at rest (66±2 vs. 32±5ms*), and also during exercise (36±4 vs. 23±5ms*). Left atrial size was enlarged in A3AR+ mice (2.0±0.2 vs 1.6±0.1mm*).

Conclusions: Increased function of adenosine receptors in mice may be a molecular model for sinus node dysfunction in man (Supported by SFB 556, project Z2).

CATHETER ABLATION OF ISCHAEMIC VENTRICULAR TACHYCARDIA

2521 Ventricular tachycardia ablation during sinus rhythm: importance of an isthmus and relation to the presence of exact pace-mapping

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Background: Substrate ablation of ventricular tachycardia (VT) can be a useful tool to treat unmappable VT.

Methods AND RESULTS: 22 Patients with cardiomyopathy referred for recurrent ventricular tachycardia ablation were evaluated. 19 Patients had ischemic cardiomyopathy and 3 patients had nonischemic cardiomyopathy. An electroanatomic system (CARTO, Biosense) was used to map the left or right ventricle during stimulation from a catheter situated in the right ventricular apex. We investigated the feasibility of identifying a conduction isthmus between 2 scar zones, its relationship with the tachycardia circuit and whether this could be used to locate successful ablation points. On voltage amplitude maps an amplitude <0.10 mV was defined as scar. A conduction isthmus was defined by the presence of several consecutive electrograms with an amplitude >=10 mV surrounded by 2 scar areas. In 9 patients (0.39) an isthmus could be recognised. Isthmus sites were characteristically zones in which multiple components ventriculograms were recorded. Pace-mapping from these sites exactly reproduced the documented clinical VT (12-lead ECG) in 7 of the 9 patients (0.77) in which an isthmus had been identified. Stimulus-QRS interval was longer than 80 ms in all the cases. Ablation was performed during sinus rhythm. Radiofrecuency was applied at points located inside isthmus zones and around them, sites where exact pace-mapping and late potentials were recorded. In the 2 patients in which mapping couldn't reproduce the clinical tachycardia, substrate ablation was attempt. Successful ablation of the clinical ventricular tachycardia was achieved in 6 of the 9 patients in which an isthmus was present.

Cases with an isthmus between scars

	VTabl successful	VT abl not successful	TOTAL
EPM	5	2	7
NEPM	1	1	2
TOTAL	6	3	9

EPM:exact pace-mapping (12 ECG-lead). NEPM: absence of an exact pace-mapping. VT abl: Ventricular tachycardia ablation.

Conclusions: An isthmus is detected in 39% of cardiomyopathy patients referred for VT ablation. Multiple component electrograms are recorded in these areas. Mapping from points inside the isthmus reproduces VT in 77% of them. Detection of conduction isthmus can be useful for VT ablation during sinus rhythm.

2522 Do all ventricular tachycardia patients need an ICD? Results from the Leiden VT ablation trial

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Introduction: ICD guidelines recommend implantation of an ICD in the majority of VT pts. Radiofrequency catheter ablation may be an alternative treatment option for selected pts. We studied long term outcome of catheter ablation procedures in pts with VT. Results: One hundred and fifty-one consecutive pts (122 male, age 57±16 years) with drug refractory VT were referred for RFCA. Underlying heart disease: ischemic heart disease (IHD, 89, 59%); arrhythmogenic right ventricular cardiomyopathy (ARVC, 32, 21%); idiopathic VT (IDIO, 30, 19%; LV: 9, 30%; RV: 21, 70%). Ablation was performed using standard mapping and ablation techniques. Results: Three hundred and six different VT's were treated (cycle length 334±87 ms, 2.0±1.4 VT/pt). Procedural success (non-inducibility of VT after RFCA) was achieved in 126 (83%) pts (70 (79%) IHD pts; 28 (88%) ARVC pts; 27 (93%) IDIO pts). Procedure-related complications (<48 hrs after RFCA) occurred in 11 (7%) pts: death 3 (2.0%); cerebrovascular accident 2 (1.3%); complete heart block 4 (2.6%); and pericardial effusion 3 (2.0%). Before discharge, 25 (17%) pts received an Implantable Cardioverter Defibrillator device (ICD). During follow-up (34±11 mos), recurrence of VT occurred in 38 (26%) pts. VT recurrences occurred in 19% of the successfully ablated pts and in 64% of the non-successfully ablated pts ($p < 0.001$). During follow-up, 12 (8%) pts died (all IHD, 8 pts due to heart failure, 1 pt died due to an unknown cause, 3 pts due to a noncardiac cause). Conclusion: RFCA of VT can be performed with a high degree of procedural success (83%). The long-term outcome of successfully ablated pts is promising with a 75% relative risk reduction compared to non-successfully ablated pts. During follow-up only 1 pt died suddenly supporting a selective ICD implantation approach in pts with hemodynamically stable VT.

2523 Linear ablation of ventricular tachycardia during sinus rhythm after identification of the infarcted area by electroanatomical voltage mapping

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Background: RF ablation of ischemic ventricular tachycardia (VT) guided by conventional activation mapping is difficult in pts having poorly tolerated VT and multiple morphologies.
Methods: We evaluated 21 pts (66±10 years, 20 men) with ischemic VT, LVEF: 33±9.6%. One pt was excluded from the study. Thirteen pts had an ICD and drug refractory VT with frequent ICD shocks (1 to 62) before procedure. The remaining 6 pts had frequent episodes of VTs (1.45/pt). All pts underwent detailed catheter mapping during sinus rhythm. Normal endocardium was defined by amplitude>1.5mV. Dense scar was defined by amplitude<0.05mV. Deliniation and size of the densely scarred myocardium was assessed using the 3-D color voltage map display (CARTO, Biosense Webster). Point-by-point RF lesions (max. 45°C [ThermoCool cath.)], 70°C [standard cath.], during max 90") to create linear lesions (LL) (around the scar, lines connecting scars, lines started from the exit point (determined by pacemapping) to normal myocardium) were performed. Site of LL was delinated by 12-lead pacemap matching VT. No drug therapy was added after ablation. ICD interrogation or visits to the First Heart Aid documented VT recurrence.
Results: Fifty-two VTs were induced in 20 pts (2.6/pt). The clinical VT was induced prior ablation in 18 pts (0.9/pt); cycle length:391±82 ms. Point-by-point RF LL applied in the left ventricle ranged from 1 to 3, average lenght = 33mm (range 9-55 mm). No adverse events were observed. In four additional patients an ICD was implanted after the procedure. Acute success was obtained in 19/20 pts (95%). In-hospital recurrence occurred in 2 pts (10%). Seventeen pts completed the 6-month follow-up. Ten pts (59%) have been free of VT. Seven pts had VT reccurrences, but these are less frequent than before ablation.
Conclusions: Linear ablation around the scar, lines connecting scars or started from the exit point of the VT to normal myocardium appears to be an effective approach to control frequent, drug refractory ischemic VT.

2524 The use of a percutaneous non-contact mapping system in targeting human ventricular tachycardia ablation: results from the first 50 patients

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The predominant treatment for human ventricular tachycardia (VT) remains palliative, utilising internal cardioverter-defibrillators (ICDs) and/or drugs. RF catheter ablation offers a potential cure but mapping the diastolic pathway (DP) of VT circuits in patients with structural heart disease has proved difficult with conventional techniques. A percutaeous, non-contact endocardial mapping system was used to guide ablation in 50 consecutive patients (age 61.7±11.8 years (mean±SD), 9 female) with VT. All patients presented with VT refractory to antiarrhythmic therapy and 78% had ischaemic heart disease. Results: 153 of 176 morphologies of VT (87%) were mapped (3.5 VTs per patient) of which 45 were clinical VT morphologies (29%). Successful ablation, defined as termination of VT or morphological change, followed by failure of inducibilty was completed in 44 patients (88%). 78/153 VT were ablated, the position of successful ablation always located within the DP. An exit site was identified in 49 out of 50 of patients (98%). DP activity was seen in 85/153 VT morphologies (56%), complete reentrant circuits were identified in 24 VT (16%), and partial DP activity mapped in a further 61 VT, traced over 27±22% of the diastolic interval (range 5-95%). 6.6±6.8 RF applications (range 1 to 34/patient) were used to ablate a total of 78 VT (4.2 applications per VT ablated) of which 22 VT were ablated by 18 RF applications on common shared diastolic pathways. No patient suffered a cardiac complication as a result of deployment of the non-contact mapping system. Follow up: 30 patients (60%) have had no recurrence of VT over follow up of 12.9±9.3 months (range 0.2 to 3.6 years). There has been a recurrence of 6/78 targeted VT (7.7%). 13 patients had ICD therapy histories available before and after ablation. ICD shock frequency was reduced from 9.1±6.3 per month (range 2-21) to 0.2±0.5 per month ($p<0.05$) over mean 14.2±15.5 months. Devices were implanted post ablation in 8 patients for fast VT/VF, with no arrhythmia detected or therapy delivered to date (mean follow-up approx 18 months). Conclusions: These data show that identification of DP activity as a target for RF catheter ablation using this system can be achieved safely and with a high degree of success. In addition, VT recurrence necessitating ICD therapy delivery, is significantly reduced.

2525 Catheter ablation of ventricular tachycardia using electroanatomical mapping and irrigated ablation technology: first results of the EuroVT study

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The Euro-VT-Study is a prospective multicenter study assessing the efficiency and safety of electroanatomical mapping (Carto, Biosense Webster) and saline irrigated ablation technology (Thermocool, Biosense Webster) for ablation of chronic recurrent ventricular tachycardia (VT). In 8 institutions, a total of 58 pts. (84% male, 64 ± 8.6 yrs.) were prospectively enrolled in the study. All pts. had coronary artery disease and remote myocardial infarction, left ventricular ejection fraction measured 29 ± 12%. The pts. had a mean of 50 ± 94 episodes of VT prior to the ablation session (range: 1 - 380, median 12 episodes), 12/58 pts. (20%) were in incessant VT. The treatment strategy for ablation was based on the induction of multiple linear lesions through target sites defined by activation mapping or complete isolation of scar areas defined by voltage mapping in the majority of pts.. A mean of 18 radiofrequency applications (range 4 - 33, duration 76 ± 31 sec.) terminated 84% of target VT's or rendered these VT's non-inducible. Major adverse events occurred in 3/58 pts. (5,2%). Two months follow-up data are complete for 27 pts.. During this early follow-up period, 10 of 27 pts. (37%) developed a recurrence of target VT or new VT's not targeted during the ablation session.
In this prospective multicenter study using electroanatomical mapping and saline irrigated ablation to treat ventricular tachycardia, an acute success rate of 84% could be achieved. However, early recurrence rate of any ventricular tachycardia during the first two months after the procedure was 37%. Detailed analysis and comparison of the different ablation strategies applied in this prospective study may provide further information to define the role of catheter ablation for the treatment of chronic recurrent ventricular tachycardia.

2526 Is the implantable cardiac defibrillator associated with a higher ventricular tachycardia recurrence after radiofrequency catheter ablation?

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Background: Some studies suggest a higher incidence of ventricular tachycardia (VT) recurrence in patients (P) with an implantable defibrillator (ICD) comparing with similar P without an ICD.
Objective: To study the influence of the ICD in the assessment of ischemic VT recurrence in our population of P who were acutely successful treated with radiofrequency catheter ablation (RFA).
Methods: Thirty-seven consecutive P (32 male, aged 63±10 years, left ventricular ejection fraction (LVEF) 33±11%) with ischemic VT in whom all mappable VTs were acutely successful ablated were included in the study. Ten P (27%) were discharged with an ICD (Group I) and the remaining P did not (Group II). No statistically significant differences were found comparing clinical and electrophysiologic characteristics (age, LVEF, spontaneous VT cycle length and inducibility of non-clinical VT at discharge) between both groups. ICD was implanted according to the physician criterion.
Results: After a long-term follow-up period (37±26 months) 12 P (32%) had VT recurrence. The presence of an ICD was significantly associated with a higher VT recurrence rate (20%/year in group I vs 7%/year in group II, $p<0.05$). Sudden death was 1%/year in group II (1 P). No statistical differences were found comparing LVEF (33% vs 34%), inducibility of non clinical VT at discharge (36% vs 30%), spontaneous VT cycle length (360±70 vs 370±79 ms and number of VT episodes previous to radiofrequency ablation (6±6 vs 6±9) between P who recurred and those who did not, respectively. A multivariate analysis, including LVEF, presence of an ICD, inducibility of nonclinical VT at discharge and number of VT episodes previous to radiofrequency ablation identified only the presence of an ICD as significant and independent predictor of VT recurrence ($p=0.04$, OR=6.7)
Conclusions: An ICD seems to be a predictor for VT recurrence. Given the absence of significant differences in clinical and electrophysiological variables, these results raise the question whether the ICD could overestimate the VT recurrence rate by treating VTs that could be non sustained.

DRUG TREATMENT OF ATRIAL FIBRILLATION

2527 Proarrhythmic events and mortality in the "Prevention of Atrial Fibrillation after Cardioversion" (PAFAC) trial

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Purpose of the study: The PAFAC trial addressed in patients with chronic atrial fibrillation (CAF) after successful direct current (DC) cardioversion (CV) the efficacy and safety of two commonly used antiarrhythmic drugs.
Methods used: 848 pts were randomised after DC-CV to either sotalol (S)(383 pts), quinidine plus verapamil (QV)(377 pts) or placebo (P)(88 pts). Study endpoint was the recurrence of CAF. All pts transmitted daily ECGs by event recorder (Tele-ECG) and performed Holter-ECGs. An independent critical event committee (CEC) reviewed all serious adverse events (SAE).
Summary of results: 20 pts (23%) in the placebo (P) group, 94 pts (25%) under S and 92 pts (24%) under QV presented SAE. The total number of SAE of 'special interest' except of death amounted to 31(3,6%) and were distributed to the P-, S- and QV-group as follows: Syncope: 1(1,1%); 3(0,8%) and 7(1,9%), TdP-tachycardia: 0; 9(2,3) and 0, ventricular fibrillation (VF):0; 2(0,5%) and 1(0,3%) and ventricular tachycardia (VT): 2(2,9%); 2(0,5%) and 4(1,1%) – in total: 3(3,4%) in the P-; 16(4,1%) in the S- and 12(3,2%) in the QV-group. 65% of life threatening arrhythmic events happened during the first 4 days. 12 death occurred during the active phase, 9 of them (75%) due to arrhythmic cause: VF (3), sudden cardiac death (5) and bradycardia (1). No death occurred in the placebo group. There were another 12 deaths after the end of the study participation only 2 being primary arrhythmic (17%).
Conclusion: Risk profiles between Sotalol and Quinidine-Verapamil were comparable with the exception of TdP occurring only under Sotalol. Total mortality during and after the active study period was comparable, however arrhythmic death occurred more frequently under study medication.

2528 Exercise performance and variability of ventricular rate in chronic atrial fibrillation patients: effects of digoxin, amiodarone and diltiazem

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Aim: We compared the effects of digoxin, amiodarone and diltiazem on heart rate control and rhythm irregularity during isotonic exercise and daily activities, in patients with chronic atrial fibrillation (AF).
Methods: 59 chronic AF pts were randomly assigned to three treatment groups for 3 months: group A (19 pts, 270 mg oral diltiazem per day), group B (20 pts, 200 mg oral amiodarone per day) and group C (20 pts, 0,25 mg oral digoxin). No differences in clinical and echocardiographic characteristics were observed among the three groups. At baseline and at 3 months follow up, Holter monitor recording and cardiopulmonary exercise test were performed to assess variability of ventricular rate and exercise capacity.
Results: Digoxin, diltiazem and amiodarone significantly decreased the mean ventricular rate during daily activities and peak exercise compared with baseline ($P < 0.05$). There were no significant differences among digoxin, diltiazem and amiodarone in the percentage reduction in ventricular rate during daily activities and peak exercise.
The exercise capacity, as measured by exercise maximal oxygen consumption, minute ventilation, ventilatory equivalent and oxygen pulse, was not significantly changed after treatment with digoxin, diltiazem or amiodarone.
The variability of ventricular rate during daily activities, as measured by standard deviation (SD) of RR intervals and the root mean square of the SD of RR intervals, was significantly reduced only after treatment with diltiazem ($P < 0.05$).AF related patients symptomatology, was also significantly improved after treatment with diltiazem.
Conclusion: Diltiazem, digoxin and amiodarone had similar effects in the control of ventricular rate and in exercise capacity. However, digoxin and amiodarone did not significantly affect rhythm irregularity and AF symptomatology in patients with chronic AF. These variables were significantly improved only after treatment with diltiazem.

2529 Rate control versus rhythm control in patients with nonvalvular chronic atrial fibrillation: the results of HOT CAFE Polish study

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HOT CAFE Polish Study (How To Treat Patients With Chronic Atrial Fibrillation) was designed to evaluate in randomized, multicenter and prospective manner risks and advantages of two therapeutical strategies in patients (pts) with chronic atrial fibrillation (CAF): rate control vs rhythm control. Inclusion criteria were: pts age 50-75 years, CAF lasting from 7 days up to 2 years with acceptable etiology of arrhythmia related to hypertension, ischemic heart disease and hemodynamic insignificant valvular heart disease or lack of assessable etiology (idiopathic AF). Our study population comprised 205 pts (F/M 71/134; mean age 61±17 year) with mean time of AF duration 273.7±112.4 days. Observation period was 12 months. 101 pts were randomly assigned to rate control (Group I). The treatment goal in this group was optimizing the heart rate (HR) frequency by 24-hours Holter monitoring using calcium antagonists (7.9%), beta-blockers (49.5%), beta-blockers+digoxin (39.6%) or digoxin by itself (3.0%). As thromboembolic prophylaxis were used oral anticoagulants (acenocumarol 74.3%) or antiplatelet drugs (aspirin 19.8%, ticlopidine 1.0%). 104 pts (F/M 33/71) were randomized to sinus rhythm (SR) restoration by DC cardioversion (CV) and its subsequent maintenance with serial antiarrhythmic drug usage (disopiramide, propafenon, sotalol and amiodarone) – rhythm control (Group II). After 12 months SR was presented in 75% pts.
Results: The incidence of hospital admission was higher in group II in comparison to group I (12% vs 74%; $p<0.001$). In both groups significant improvement of heart failure symptoms estimated by NYHA scale was observed during first 2 months ($p<0.02$ and $p<0.001$). In group II exercise tolerability measured by maximal workload during treadmill test significantly improved (5.2±5.1 vs 7.6±3.3 MET; $p<0.0001$). SR restoration influenced improving LV function and increasing value of shortening fraction (29±7% vs 31±7%; $p<0.01$). No thromboembolic complications were observed in pts left with AF. 3 pts suffered ischemic stroke in group II: 2 cases were associated with CV, the third one with late AF recurrence.
Conclusion: HOT CAFE Polish Study did not reveal the significant differences in two treatment strategies in CAF in 12 months follow-up.

2530 Class IC or amiodarone induced atrial flutter during chronic treatment of AF: long-term follow-up of hybrid pharmacological and ablative therapy

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Patients (pts) chronically treated with amiodarone or class IC antiarrhythmic drugs (AAD) for recurrent atrial fibrillation (AF), can experience conversion of AF to atrial flutter (AFL) in about 5-22%. In these pts, hybrid ablative and pharmacological treatment can be effective in maintaining sinus rhythm (SR). The aim of this study was to evaluate the long-term results of this therapeutic strategy. Methods: From October 1996 to May 2001, 101 pts (75 male, mean age 62±10 years) chronically treated with class IC AAD (57 pts, 56%), amiodarone (37 pts, 36%) or amiodarone plus IC AAD (7 pts, 8%) had conversion of AF into typical AFL. Mean AF duration was 5.4±9 years (median 2 years). A mean of 2±0.9 drugs had been ineffective in maintaining SR. History of more than 10 episodes of AFL was present in 24.7% of pts. Seventy-eight pts (78%) had structural heart disease (14 ischemic, 28 hypertensive, 13 valvular, 23 other). Mean LVEF was 59±10% and mean left atrial diameter was 4.4±0.5 cm. All pts underwent radiofrequency ablation of cavo-tricuspidal isthmus maintaining previous AAD at discharge. All pts underwent baseline evaluation, ECG and Holter monitoring at 1, 3 and every six months. These evaluations were also performed if symptoms were referred. Results: AFL ablation was effective in 97 pts (97%) achieving bidirectional isthmus conduction block. In 3 pts bidirectional isthmus block was reached after a second procedure performed for AFL recurrence. Complications were observed in 2 pts (2%): 1 pts had complete AV block and 1 deep vein thrombosis. After a mean follow-up of 20±11 months 51 pts (50.5%) maintained SR continuing the same drugs as before ablation. AFL recurred in 7 pts (7%). The actuarial recurrence rate of AFL/AF was 31% at 1 month, 46% at 6 month, 49.5% at 1, 2, 3 and 4 years. Conclusions: Hybrid pharmacological and ablative therapy of class IC or amiodarone AFL is effective in preventing recurrence of AFL and AF. During long-term follow-up a low risk of AF recurrences was observed in pts treated with hybrid therapy, that were event-free for more than 6 months after AFL ablation.

2531 Comparison of acute and long-term effects of Ibutilide and verapamil for the management of immediate recurrence of atrial fibrillation

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Immediate recurrence of atrial fibrillation (IRAF) after successful transthoracic cardioversion (TCV) is a common clinical finding. There is evidence that atrial remodeling is due to intracellular calcium (iCA) overload and that calcium channel blocking (CCB) agents attenuate these electrophysiological changes. Ibutilide (Ibu) is a class III drug that has recently been shown to markedly facilitate TCV. The aim of this prospective study was to determine the incidence of IRAF, to compare the efficacy of i.v. verapamil (Ver) and i.v. Ibu for the prevention of IRAF, and to compare the long-term AF-recurrence rate of pts with and without IRAF.

Methods: TCV was performed in 223 pts using a step-up protocol (100J-200J-300J-360J). After successful TCV, pts were monitored for 30 minutes. If two IRAFs occurred, pts were randomized to i.v. Ver (0.15 mg/kg) or i.v. Ibu (1 mg) 10 minutes prior to another TCV attempt. In the event of another IRAF, pts crossed over to the other treatment arm and TCV was repeated.

Results: A total of 21 pts (9.4%, 17 males, age 59±12 yrs, LVEF 0.52±0.08) had IRAF 86±51 sec. after TCV. The mean duration of AF was 28±37 weeks. Six pts (29%) were on amiodarone, 10 pts on b-blockers, and four pts on a CCB. One pt was not randomized because the LVEF was <0.3. Eleven pts were randomized to Ver. 8/11 pts (73%) experienced another IRAF after 18±10 sec and 7/8 pts crossed over to the Ibu arm. One (14%) of these patients had another IRAF. Nine pts were randomized to Ibu and 2 (22%) of these had another IRAF, which was significantly less often than in the Ver group (P=0.02). One of the latter pts received Ver and had no further IRAF. Including the pts who crossed over, IRAF occurred in 3/16 pts (19%) after administration of Ibu, compared to 8/12 pts (67%) in the Ver arm (p=0.01). 18/223 (8%) in the non-IRAF and 2/20 pts (10%) in the IRAF group were lost to follow-up. After a mean follow-up of 27±30 weeks, 5/18 pts (28%) in the IRAF and 73/185 (39%) in the non-IRAF group remained in sinus rhythm (p=0.3).

Conclusions: The incidence of IRAF is 9.4%. Ibutilide is significantly more effective than verapamil in treating IRAF. Since the long-term AF recurrence rate does not differ significantly in pts with and without IRAF, it is worthwhile to treat IRAF.

2532 Atrial fibrillation in hypertrophic obstructive cardiomyopathy: prevalence, symptoms and quality of live

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Background: At present influence of atrial fibrillation (AF) on symptoms and quality of live (QoL) in hypertrophic obstructive cardiomyopathy (HOCM) is not clearly defined. Corresponding to prevalence of AF in HOCM only few reports are available.

Patients and Methods: The study population consisted of 80 consecutive patients (pts, 38 f, mean age 56 ± 17 y) with severe symptoms due to HOCM, who were treated by transcoronary ablation of septal hypertrophy (TASH). Prevalence of AF was detected by three holter ECG registrations before and 2 weeks respectively 7 months after TASH. Symptoms and QoL were evaluated by a standardised and validated questionnaire before and in long term follow up after TASH. Pts in AF and sinus rhythm (SR) were compared with regard to symptoms and QoL.

Results: The overall prevalence of AF was 29%. Paroxysmal AF in 17 pts (21.3%) and persistent AF in 5 pts (6.3%) were detected. Only 1 pt (1.3%) suffered from permanent AF. Symptoms due to AF were present in 12 pts (52.6%). Mean follow up after TASH was 32 ± 13 months. Both groups (AF and SR) showed significant improvement of symptoms, exercise tolerance and QoL, but there was no difference between the groups with AF and SR. Although those 6 pts with permanent or persistent AF at baseline showed superior improvement by TASH than the other 74 pts (QoL-score 4.0 ± 0 vs. 3.3 ± 0.7, p = 0.017).

Conclusions: Prevalence of AF is high (29%) in HOCM associated with severe symptoms. Nevertheless in the vast majority paroxysmal AF is present (21%). Half of patients suffered from symptoms due to AF. TASH improves QoL in both AF and SR patients. In particular HOCM pts with persistent and permanent AF profit by TASH

YOUNG INVESTIGATORS' AWARD SESSION (CLINICAL SCIENCE)

2533 Prognostic impact of matrix metalloproteinase (MMP)-9 plasma concentration and genetic variation of the MMP-9 gene

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Introduction: As part of an ongoing inflammatory process within the atherosclerotic plaque Metalloproteinases (MMP) probably play a central role in atherosclerotic plaque destabilization. MMP-9 underlies in part genetic regulation. A functional G/A mutation within the MMP-9 binding domaine leads to aminoacid exchange (MMP-9/R279Q) and probably influences the MMP-9 enzyme activity. We evaluated first the relationship between MMP-9 plasma levels and future cardiovascular mortality and second the influence of the newly detected MMP-9/R279Q mutation on this relationship.

Methods: In 1176 patients with documented CAD MMP-9 plasma levels [ng/ml] were measured and the MMP-9/R279Q genotype determined. 1169 pts (99.4%) had a follow up (f/u) after a median of 4.1 (maximum 5.2) years.

Results: During f/u 127 pts died, 100 due to cardiovascular causes. Increasing quartiles of MMP-9 were associated with an 1.4 (95% CI 1.2 to 1.7, P<0.0001) increase in risk. The highest quartile compared to the lowest revealed a 2.7 (95% CI 1.5 to 5.1, P=0.002) increase in risk to suffer from future cardiovascular mortality. These associations were hardly weakened by controlling of most potential confounders. Most importantly, the association was strongly restricted to A allele carriers of the MMP-9/R279Q genotype(58.2% of the study population, P for interaction = 0.03, see Table).

MMP-9	Q1	Q2	Q3	Q4	P-univ.	P-multiv.
range [ng/ml]	<33.4	33.4 - 49.5	>49.5 - 73.8	>73.8		
all pts	4.4	6.2	9.6	14.1	<0.0001	0.002
MMP-9/GG	3.0	7.8	5.3	6.0	0.4	0.7
MMP-9/GA + AA	2.6	4.3	8.8	13.1	<0.0001	0.002

P values are given as P for trend; P multiv. controlled for age, sex, classical risk factors, clinical and therapeutic features including unstable angina, extent of vessel disease, history of MI, betablocker and statin therapy, interventional therapy, and ejection fraction.

Conclusion: In this large prospective cohort of pts we could demonstrate for the first time that plasma MMP-9 concentration is a strong and independent predictor of future cardiovascular mortality. This association was strongly restricted to A allele carriers of the newly detected, functional MMP-9/R279Q genotype. These findings should further be evaluated with special regard to newly developed MMP-9 inhibitors.

2534 Gadolinium enhanced MRI detects abnormal myocardium in HCM which correlates with clinical risk

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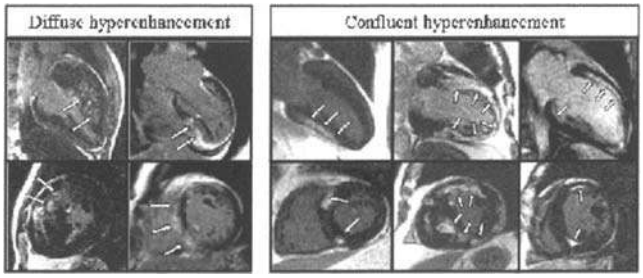
Background: Hypertrophic Cardiomyopathy (HCM) may be complicated by sudden death in the young and heart failure in the old. It is thought that myocardial fibrosis is a key underlying pathological process. Gadolinium enhanced Cardiovascular Magnetic Resonance (CMR) can demonstrate fibrosis in myocardial infarction. We hypothesised that it could demonstrate abnormal myocardial hyperenhancement in HCM and that it would be linked to clinical events.
Methods: A blinded prospective study. 40 HCM patients were selected for the number of clinical risk factors for sudden death and for the presence or absence of adverse remodelling on serial echocardiography (progressive disease). Gadolinium enhanced CMR was performed.
Results: 31(77%) patients had abnormal hyperenhancement. The mean percentage of LV hyperenhancement was 10.7%(0-40%). There was more hyperenhancement in patients with progressive disease (26% vs 8.4%, p=0.0004), and a trend in patients at higher risk of sudden death (13.6% vs 9.2%, p=0.12). Subgroup analysis demonstrated that in young patients (<40), there was more hyperenhancement in patients at higher risk of sudden death (16.3% vs 2.53%, p=0.03) whilst in older patients more hyperenhancement in patients with progressive disease risk (26.5% vs 5.4%, p=0.0005). Different patterns of hyperenhancement (myocardial phenotypes) were seen which associated with different clinical parameters (clinical phenotypes).



Types of hyperenhancement in HCM.

Conclusion: Gadolinium enhanced CMR can demonstrate abnormal myocardium in HCM. This has the potential to classify and follow HCM disease progression in-vivo and serve as a clinical risk factor for sudden death and heart failure.

2535 Relationship between pressure derived collateral flow and angiographic TMP grading during rescue angioplasty

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Introduction: In patients with chronic stable angina, pressure wire derived fractional collateral flow (Qc/Qn) of >0.28 has been associated with improved outcomes following percutaneous coronary intervention (PCI). The utility of the pressure wire derived parameters in patients with acute myocardial infarction (AMI) may be compromised by microvascular dysfunction.
Objective: To assess the relationship between maximum recruitable Qc/Qn and TIMI myocardial perfusion (TMP) grading in the setting of rescue PCI.
Methods: 28 consecutive patients underwent rescue PCI for failed thrombolysis based on standard ECG criteria. A pressure wire (RADI, Sweden) was used as the primary guide wire. Fractional flow reserve (FFR), coronary wedge pressure (Pw) and Qc/Qn pre PCI, during balloon inflation and post PCI were estimated under conditions of maximal hyperaemia induced with intracoronary adenosine. Pre and post PCI TIMI flow and post PCI TMP grading were assessed by a physician blinded to the study protocol.
Statistics: Maximum recruitable Qc/Qn (during balloon inflation) were compared for the different TMP grades. Qc/Qn during balloon inflation and post PCI Qc/Qn were compared with pre PCI values. The students t test was used to assess significance.
Results: The pressure wire was successfully manipulated in all patients. Pre PCI TIMI flows were as follows: 14 TIMI 0-1, 11 TIMI 2 and 3 TIMI 3. Post PCI, TIMI 3 flow was established in 24 patients with 4 only achieving TIMI 2 flow. Post PCI TMP grades were as follows: 21 patients (75%) TMP 0 grade and 7 TMP 1-2 grade. The pressure wire derived parameters are detailed in the table. There was an inverse relationship between maximum recruitable Qc/Qn and TMP grading [p=0.003;mean(SD)Qc/Qn of 0.28(0.1) with TMP 0 grade versus 0.16(0.08) with TMP 1-2 grades]
Conclusion: The pressure wire can be used as the standard guide wire during rescue PCI. Higher pressure derived fractional collateral flow (Qc/Qn) is associated with angiographic evidence of microvascular dysfunction.

	FFR - mean (SD)	Qc/Qn - mean (SD)
Pre PCI	0.52 (0.2)	0.15 (0.1)
Occlusion		0.24 (0.1) p<0.001 vs pre PCI
Post PCI	0.94 (0.04)	0.03 (0.03) p<0.001 vs pre PCI

2536 Endothelin-1 is involved in coronary no-reflow

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Background: No-reflow (NR) is a multifactorial condition comprising an acute reduction in coronary flow in the absence of epicardial vessel obstruction. Current concepts invoke vasoconstriction as a key factor in NR. Therefore, we investigated the role of endothelin-1 (ET-1), a potent vasoconstrictor peptide that is abundant in atherosclerotic lesions. Methods and Results: Initial experiments utilized homogenates from atherosclerotic arteries and confirmed the presence of ET-1 antigen. In the next step, right coronary arteries (RCAs) from 6 domestic pigs were selectively injected with 2ml each of homogenized atherosclerotic human plaque material containing 6.9±4fmol/ml ET-1. Angiographically, flow was compromised in 5 of 6 animals. Fractional flow reserve (FFR) dropped from 2.0±1.0 to 0.8±0.2 (p=0.0045) with a marked decrease of baseline flow immediately after the injection. The same effect was achieved with direct injection of 0.15μg/kg purified human ET-1 in two pigs. To examine the role of ET-1 in human acute coronary NR, coronary blood was drawn from patients undergoing percutaneous interventions using the distal protection devices PercuSurge GuardWire (n=10), the X-Sizer Catheter System Thrombus Removal Device (n=9) and Angioguard (n=2). Fine particulate plaque material that was recovered from each of those devices contained on an average 0.13±0.18fmol ET antigen/40ml whole blood.
Conclusions: The data suggest that ET-1 is released into the coronary circulation from ruptured atherosclerotic plaque and contributes to the NR phenomenon, possibly by inducing spasm in the depending coronary microvasculature. The data suggest that ET-receptor antagonists could become powerful tools in the prevention and treatment of NR or slow flow.

2537 Histologic findings in patients with clinical and instrumental diagnosis of arrhythmogenic right ventricular dysplasia

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Objectives: The value of endomyocardial biopsy compared with other non-invasive and invasive cardiac exams in the diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) is still controversial. We report the biventricular histologic findings of 30 patients (pts) with a diagnosis of ARVD established by applying the conventional clinical and instrumental criteria.
Methods and Results: Among 78 consecutive pts with ventricular arrhythmias, normal left ventricular (LV) global function and coronary arteries, 30 (38%) had arrhythmias with left bundle branch block morphology and right ventricle (RV) abnormalities. All pts underwent non invasive (2D-echo, magnetic resonance) and invasive cardiac studies (including LV, RV angiography with biventricular endomyocardial biopsy and electrophysiologic study). Endomyocardial biopsies were performed in the septal-apical region of the LV and in specific sites of the RV (i.e. apex, anterior free wall, inferior wall). On the basis of electrocardiographic, arrhythmic and morpho-functional criteria all pts would have received the diagnosis of ARVD. At histology, the diagnosis of ARVD was confirmed only in 9 pts, while in 21 pts a focal inflammatory infiltrate with necrosis of the adjacent myocytes diagnostic for myocarditis was present in all RV specimens and even in the LV biopsies from 10 pts. No fatty tissue infiltration was observed in myocarditic pts, while foci of inflammatory cells were present both in the RV and LV of 4 pts with ARVD. No statistically significant difference was found between pts with ARVD and with myocarditis regarding the severity of ventricular arrhythmias (p=0.9359), ECG depolarization and repolarization abnormalities (p=0.92), structural RV abnormalities, including global or regional RV dilatation (p=0.8731) and dysfunction (p=0.8731). Finally, magnetic resonance imaging showed the typical signal of high intensity in T1 weighted images in 66% of ARVD pts and in 62% of myocarditic pts (p=0.8687).
Conclusions: An elective RV myocarditis can mimic an ARVD. Histology seems the most correct diagnostic tool with significant impact on prognosis and treatment.

PULMONARY HYPERTENSION

2559 Relationship of exercise capacity to echocardiographic parameters in patients with pulmonary arterial hypertension: the BREATHE-1 echo substudy

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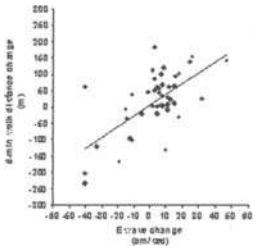
Background: Pulmonary arterial hypertension (PAH) is associated with abnormalities in cardiac structure and function which contribute to impaired functional capacity. We evaluated the relations of echocardiographic and Doppler measures to exercise performance in a subgroup of 85 patients with WHO class III and IV PAH enrolled in the prospective, multicenter, double blind, placebo-controlled BREATHE-1 study.

Methods: Patients had primary pulmonary hypertension or PAH associated to scleroderma. 29 patients received placebo and 56 the orally active dual endothelin receptor antagonist bosentan in a 1:2 randomization procedure. 6-minute walk tests and echocardiograms were performed at baseline and after 16 weeks of treatment.

Results: Compared to placebo, bosentan resulted in an increase of 37 m in 6-minute walk distance (p=0.036) and an increase of 0.4 l/min/m^2 in Doppler-derived cardiac index (p=0.007). On the baseline evaluation, multiple stepwise regression analysis showed that the distance walked in 6 min was correlated with right ventricular (RV) end-diastolic area (r=-0.39, p=0.009), Doppler RV index (r=0.35, p=0.022) and left ventricular (LV) end-diastolic area (r=0.35, p=0.022). Serial changes of distance walked in 6 min from baseline to week-12 were correlated on multivariate analysis with changes of LV early diastolic filling (E wave) velocity (r=0.65, p<0.001)(Fig 1) and with changes of pericardial effusion score (r=-0.43, p=0.004).



Conclusions: In patients with PAH, poor exercise tolerance is correlated with echocardiographic evidence of RV dilatation and failure and of LV reduction. Serial improvements in exercise capacity are related to improved early LV filling, and pericardial effusion score.

2560 Pharmacokinetics and safety of bosentan, an oral dual endothelin receptor antagonist in children with pulmonary arterial hypertension: BREATHE-3

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Background: Bosentan, an orally active dual endothelin receptor antagonist, significantly improved exercise capacity and hemodynamics in two double-blind, placebo-controlled studies in adults with pulmonary arterial hypertension (PAH). Therefore, BREATHE-3 was designed to evaluate tolerability and safety of bosentan in children with PAH.

Methods: This open-label, uncontrolled single and multiple-dose study assessed pharmacokinetics, tolerability and safety of bosentan in children 4-17 years of age with PAH. Children with and without epoprostenol were stratified according to weight to 3 different doses; n=6 per group. Children with PPH or PAH associated with congenital heart defects (functional class II or III) who were clinically stable for at least 3 months prior to enrollment with a systemic arterial oxygen saturation > 88% were studied. Patients with ALT/AST levels of > 2xULN were excluded. At baseline and after 12 weeks of treatment,hemodynamic measurements and pharmacokinetic parameters (e.g. Cmax, tmax, t1/2, AUC0-μ, AUCt, CL/F) were recorded for each child. Safety was evaluated by laboratory tests and adverse event recording. Cardiopulmonary exercise testing was performed on children > 8 years old at baseline and after 12 weeks.

Results: Eighteen children were enrolled (10 with and 8 without epoprostenol), 10 female, 8 male with a mean age of 12 ± 4 years. The hemodynamic and exercise results (mean ± SD) are shown below. Following the week 12 assessment, patients continued open label treatment with bosentan and the dose of epoprostenol was decreased in all four children in whom this was attempted without any apparent change in overall clinical status.

	Peak VO2 (ml/min) N=12	Six Minute Walk Distance (m) N=12	PAPm* (mmHg) N=18	CI (L/m/M2) N=17	PVRI (units · M2) N=18
Baseline	798 ± 401	492 ± 68	58 ± 16	4.1 ± 1.6	14 ± 7
Week 12	841 ± 495	492 ± 92	51 ± 20	4.6 ± 1.3	11 ± 9

*p=0.004 vs. baseline

Conclusion: BREATHE-3 provides valuable data regarding the tolerability and safety for bosentan, an orally active, dual endothelin receptor antagonist, in pediatric patients with PAH. This study suggests that the addition of bosentan to epoprostenol may allow a subsequent decrease in dose of intravenous epoprostenol, potentially decreasing the prostanoid-related side effects and thereby improving the risk-benefit profile for patients with PAH.

2561 Improved oxygenation relieves baroreflex dysfunction in Andean altitude natives with chronic mountain sickness

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Andean altitude natives with chronic mountain sickness (CMS) have neurologic and autonomic symptoms at altitude, which disappear at sea-level. To test whether baroreflex abnormalities contribute to CMS, we measured RR interval (RR), systolic blood pressure (SBP), and respiratory variabilities, by spectral analysis, in 31 natives of Cerro de Pasco (CP), (4338m, Peru), with variable degrees of CMS (CMS score 4-26) at baseline and during carotid baroreflex modulation by neck suction (NS) at 0.1Hz (LF, sympathetic modulation on SBP, vagal and symapthetic on RR), and at 0.2Hz (HF, vagal modulation on RR), in CP, before and during normoxia (CP+ox), and in Lima, sea-level, after one night sleeping in normoxia (SL) and during hypoxia. Subjects were divided according to CMS score (CMS+: =/> 12, N=15, CMS-: <12, N=16).

In CP, compared to CMS-, CMS+ showed reduced resting HF (p<0.05), reduced HF-NS modulation on RR (p<0.02), and reduced LF-NS on RR (p>0.02) but not on SBP, indicating preserved sympathetic modulation but reduced cardiac baroreflex vagal modulation. CP+OX increased RR modulation in CMS-, so all differences became more significant. At SL, CMS score dropped to 2.9 ±0.5 (p<0.0001); RR resting and NS-induced HF increased (p<0.01) in CMS+, attenuating the differences with respect to CMS- (p<0.05 during both LF-NS and HF-NS). Hypoxic gas mixture administrated at SL restored the differences seen at CP in the RR response to either LF-NS or HF NS (both p<0.01). Resting HF (p<0.01) and HF-NS in RR correlated inversely with CMS score (p<0.0002) in CP.

Vagal and baroreflex dysfunction may be implicated in the origin of CMS symptoms; this can partially reverse with improved oxygenation.

Abstract 2562 – Table

Parameter	APE whole group n=64	Survivors n= 56	Nonsurvivors n=8	Odds ratio (95% CI)
Repetitive cTnT > 0.1ng/ml [%]	50.0	42.8	100	21 (1,2-389) #
TVPG [mmHg]	42.5 ± 14.0	39.1 ± 12.0	7.4 ± 16.7	.09 (1.02-1.16) *
Age [yrs]	61.3 ± 17.0	59.2 ± 16.0	76.0 ± 16.0	1.09 (1.01-1.10) *
BPs [mmHg]	122 ± 22	121 ± 21	128 ± 27	1,01 (0.98-1.05) NS
HR [1/s]	100 ± 19	99 ± 18	112 ± 24	1.04 (0.99-1.08) NS
RV/LV	1.03 ± 0.29	1.03 ± 0.30	1.01 ± 0.29	1.07 (0.80-1.06) NS
Thrombolysis (%)	12.5	12.5	12.5	NS

# p< 0.005, * p< 0.05

2562 Cardiac troponin T (cTnT) monitoring identifies high risk group among patients with acute pulmonary embolism (APE)

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Identification for thrombolysis in normotensive pts with APE based on the presence of right ventricular (RV) strain at echocardiography is controversial. We checked whether monitoring of cTnT might help in risk stratification detecting patients with ongoing RV myocardial injury.

Material and methods: We studied 64 normotensive pts (30F, 34 M) aged 61.3+17.0 yrs with APE. All pts underwent TTE for of RV strain. Plasma cTnT (ELISA, Roche, detection limit >0.1ng/ml) were measured at the admission, and subsequently 3 times in 6 hours intervals. Managing physicians were unaware of cTnT results, therefore troponins levels did not influence the therapy. Anticoagulation only was used in 87.5% pts, while 12.5% pts received thrombolysis.

Results: During hospital observation 8/64 pts died. (in hospital mortality 12,5%) due to irreversible RV failure in 6 pts, in 2 others recurrent fatal APE was diagnosed. CTnT was elevated at the admission in 45.3% pts. Repetitive assays showed elevated cTnT in additional 3 pts. All death occurred in cTnT positive group, however in 1 case first three assays were negative. Odds ratio analysis revealed that elevated plasma cTnT mostly affected short term prognosis. Older age, decreased blood pressure and tachycardia only moderately influenced the outcome. There were no differences in RV/LV ratio between survivors and nonsurvivors. However, elevated tricuspid valve peak systolic gradient moderately indicated worse prognosis.

Conclusion: Patients with APE and elevated cTnT plasma levels at repetitive assays are at significant risk of fatal outcome and should be regarded for high risk group. Clinical and echocardiographic parameters are of limited value in the risk stratification among normotensive patients with APE.

2563 Prevalence and outcome in systemic sclerosis associated pulmonary hypertension: a four-year follow-up study

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Objective: Determine the prevalence of Systemic Sclerosis-related Pulmonary Hypertension (SSc PHT) and identify predictors of mortality in a large patient cohort.

Design: Prospective 4-year follow-up study between March 1997-September 2001.

Setting: A large teaching hospital providing a national referral service for the management of Systemic Sclerosis.

Patients: 950 patients with Systemic Sclerosis under regular follow up at the Royal Free Hospital, London. All patients were screened for pulmonary hypertension using a combination of echocardiography, lung function testing and clinical assessment. Patients with suspected elevated pulmonary artery systolic pressures (PASP) of>35 mmHg on echocardiography and/or diffusing capacity (DLCO)<40% expected on lung function tests or dyspnoea of unexplained cause underwent right-heart catheterisation.

Intervention: Right-heart cardiac catheterisation with haemodynamic measurements at baseline and after acute vasodilator challenge. All patients were actively treated with warfarin, calcium channel blockers, and prostacyclin therapy in accordance with current best practice.

Results: The prevalence of pulmonary hypertension was 12% (118/950) by right-heart catheter. Survival was 78% at 1-year, 52% at 2-years and 40% at 3 years from the diagnosis, with no significant difference between those with and without pulmonary fibrosis. Our survival data, derived from a patient cohort treated with best-available therapy significantly differed from previous studies that had suggested 1,2 and 3-year survivals of 45%, 36% and 28%. The main cause of death was right ventricular failure. Elevated right atrial pressure (P=<0.01), low cardiac index (P=<0.001), reduced mixed venous oxygen saturations (P=0.05) and higher levels of pulmonary pressure (P=0.05) each independently predicted an increased mortality. Absence of vasodilator response on acute challenge did not predict outcome.

Conclusions: The prevalence of SSc-related pulmonary hypertension was lower than expected from previous studies that have relied on echocardiographic data. Measures of right ventricular function (RAP,CI, mPAP)predicted an adverse prognosis. The future outlook is encouraging with improvement in survival compared to historical controls

2564 Sildenafil lowers pulmonary vascular resistance in children after heart surgery

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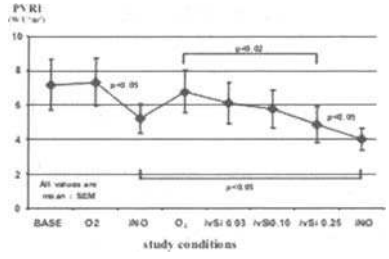
Background: Children with elevated pulmonary vascular resistance (PVR) after congenital heart surgery show increased postoperative morbidity and mortality. Inhaled nitric oxide (iNO) selectively lowers pulmonary vascular resistance (PVR)in patients, but it has important side effects which limit its use. Sildenafil (Si) enhances the NO-cGMP pathway by blocking phosphodiesterase typ 5 (PDE-5), thus augmenting the bioavailability of cGMP, the second messenger of NO. We studied the effects of intravenous Si (ivSi) on PVR in children after heart surgery with cardiopulmonary bypass.

Method: 8 infants (age 3.8±1.2 months, weight 4.6±0.6 kg) with preoperative pulmonary hypertension due to intracardiac shunting defects and an elevated risk of postoperative increased PVR were included. All were examined in the early postoperative period while they were still sedated and paralysed. PVR was measured using the direct Fick principle with measurement of oxygen consumption by respiratory mass spectrometry. Measurements were performed at baseline, with FiO2 =0.65, and then with the addition of iNO (20ppm) before and after ivSi (cumulative doses of 0.03, 0.10 and 0.25 mg/kg).

Results: No clinically relevant systemic hypotension or other side effects occurred during ivSi. PVR fell with iNO both before and after PDE-5 blockade. However, ivSi alone lowered PVR to a similar level as iNO. The combination of iNO and ivSi produced the lowest PVR (see Figure 1).



Conclusion: Pulmonary endothelial dysfunction in postoperative children with a decreased endogenous NO-production may be ameliorated by increasing cGMP-availability by PDE-5 blockade. Sildenafil may be useful as an additional treatment option for patients with increased pulmonary vascular resistance.

CLINICAL RELEVANCE OF CIRCADIAN VARIATIONS OF BLOOD PRESSURE AND HEART RATE

2565 Heart rate and heart rate variability in white-coat hypertension

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The aim of the study was to assess heart rate and heart rate variability among patients with white coat hypertension.

Methods: 168 persons over 30 years old, entered the study. In each subject, conventional blood pressure was measured during three separate visits, 5 times on each visit. Arterial hypertension was diagnosed if the patient was receiving antihypertensive treatment or average blood pressure (BP) measured on three separate occasions exceeded 140/90 mmHg. White coat hypertension was defined as BP>140/90 mmHg only at the first visit, in untreated subjects. The group was subdivided into three subgroups: Hypertensives (group 1): n=88, age=45.6±12.6 years, BMI=28.7±4.6 kg/m^2, BP at the first home visit=157.5±19.3/96.9±10.6 mmHg; subjects with white-coat hypertension (group 2): n=37, age=43.5±4.5 years, BMI=27.4±4.5 kg/m^2, BP at the first home visit=144.0±7.9/89.7±6.9 mmHg; and normotensives (group 3): n=43, age=43.3±11.7 years, BMI=28.6±4.1 kg/m^2, BP at the first home visit=120.0±19.3/75.4±8.4 mmHg.

In each subject, in standardised laboratory conditions, 30 min ECG was recorded: 15 min supine, 15 min standing, using a validated device - CardioPSA System, Medatec. Fast Fourier transform was used to obtain power spectrum analysis (PSA) of heart rate variability components: total variance, low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.40 Hz) values.

Results from supine recordings are summarised in the table. Similar findings were observed in the standing position.

	Hypertensives (n=88)	White-coat hypertensives (n=37)	Normotensives (n=43)
RR interval (ms)	941.0±147.7*	938.5±123.6*	915.3±127.7
Total variance (ms2)	2531.9±4956.9†	2871.8±3656.2†	4271.3±4597.9
HF component (%)	38.2±13.3†	38.3±14.7†	35.4±13.7
LF component (%)	45.7±17.7*	47.7±16.6	53.2±17.5

* $p<0.05$ vs normotensives;† $p<0.01$ vs normotensives

Conclusion: Patterns of heart rate and heart rate variability in subjects with white coat hypertension are similar to these observed among hypertensives, with increased heart rate, decreased total variance and decreased parasympathetic activity (HF component). These data suggest impaired sympatho-vagal balance in white-coat hypertension.

2566 A new index for the quantitative evaluation of the cardiovascular effects of obstructive sleep apnea syndrome

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Obstructive Sleep Apnea Syndrome (OSAS) is associated with increased cardiovascular (CV) morbidity and mortality, due to frequent nocturnal blood pressure (BP) peaks that follow apneic episodes. OSAS severity is usually assessed by the apnea-hypopnea index (AHI, n of episodes/h) which quantifies the degree of respiratory impairment but not the negative effects of OSAS on the CV system, largely due to hypertensive peaks. Aim of this study is: 1)to propose a new index to quantify the severity of OSAS CV effects, 2)to compare the values of this index in OSAS and healthy volunteers and 3)to evaluate its changes under acute and chronic nasal continuous positive airway pressure (CPAP)tretment. The new index, Cross-Power Index (CPI), quantifies the beat by beat effects of changes in oxygen saturation on changes in systolic(S)BP, and is defined as the integral of the cross-spectrum modulus between SBP and oxygen saturation (SaO2) over a broad range of frequencies where SaO2 and SBP spectral powers are linearly correlated. In 15 severe OSAS patients (AHI>50, age range 38-65 years) and in 7 normal volunteers of comparable age, a complete multichannel polysomnography (PSMG) was performed overnight. PSMG was repeated in 6 severe OSAS patients under acute CPAP treatment, and in 10 OSAS patients when discontinuing CPAP after 6 months of regular treatment. To compute CPI only SBP and SaO2 were considered, by computing their broad band spectral powers. The cross-spectrum between SBP and SaO2 was computed by the Welch method. CPI was calculated by the averaged cross-spectrum modulus.

In the control group CPI was invariably lower than 5 mmHg (90% tolerance limits:2.6-4.8 mmHg). In OSAS CPI was markedly and significantly greater (tolerance limits 32-97 mmHg). In the 6 OSAS patients evaluated after acute CPAP, CPI decreased on average from about 60 to values <20 mmHg (normal levels reached in 4 out of 6 cases. In the 10 OSAS patients evaluated after chronic CPAP was discontinued, AHI returned to pre-treatment high values, while CPI remained significantly reduced by more than 50% as compared to before treatment.

Thus, high CPI values may detect severe OSAS patients with no need of complete PSMG, but only of continuous SBP and SaO2 monitoring. CPI may complement AHI in OSAS diagnosis by quantifying its cardiovascular effects, and may assess the efficacy of treatment over and above the information provided by AHI. Given the simpler setup required,CPI might more easily allow to screen the hypertensive population, in which OSAS is highly prevalent and represents an additional risk factor.

2567 Strong genetic effect on ambulatory pulse pressure in a sample of Polish twins

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Background and Objective: Emerging data show pulse pressure is an important prognostic marker of cardiovascular risk. We determined genetic and environmental contributions to pulse pressure in a group of Polish twins aged 18-45 years.

Design and methods: 39 monozygotic (MZ, age 33±7 years, BMI 23±3 kg/m^2) and 37 same-sex dizygotic (DZ, age 36±7 years, BMI 24±4 kg/m^2) twin pairs recruited by inviting letters were studied, including 30/152 (19.7%) subjects with hypertension (defined as high blood pressure or antihypertensive treatment). Zygosity was determined with microsatellite markers and a questionnaire. Systolic (SBP) and diastolic blood pressure (DBP) were measured clinically and by ambulatory blood pressure monitoring (ABPM, SpaceLabs 90271). Pulse pressure (PP) was calculated as the difference between SBP and DBP. Statistical analysis was performed using the SPSS program and parameters of the genetic models were estimated by model fitting and path analysis technique using the LISREL 8 program.

Results: Mean 24-hour blood pressure was 116/74±10/8 mmHg in MZ twins and 121/76±10/7 mmHg in DZ twins. We found strong genetic effect on pulse pressure derived from ABPM (60%-80% of PP variability) that was larger than genetic effect on pulse pressure measured clinically (PP clinic, 35% of PP variability). Effect of genetic factors on daytime values (PP day) was similar to the effect on 24-hour mean values (PP 24-hour) and larger than the effect on nighttime values (PP night). SBP and DBP (clinic and ABPM) were also significantly influenced by genetic factors. Estimates of genetic (h2), shared environmental (c2) and unshared environmental (e2) effects, goodness of fit statistics, and correlation coefficients for MZ (rMZ) and DZ (rDZ) twin pairs are shown below (*ADE model).

	h2	c2	e2	chi2(df)	p	rMZ	rDZ
PP clinic	0.35	0.65	0.00 (4)	1.00	0.35	0.18	
SBP clinic	0.53	0.47	7.12 (4)	0.13	0.53	-0.12	
DBP clinic	0.62	0.38	2.65 (4)	0.62	0.67	0.18	
PP 24-hour	0.77	0.23	0.00 (3*)	1.00	0.77	0.26	
SBP 24-hour	0.73	0.27	2.37 (4)	0.67	0.71	0.34	
DBP 24-hour	0.47	0.19	0.34	1.73 (3)	0.63	0.66	0.37
PP day	0.80	0.20	0.00 (3*)	1.00	0.80	0.24	
PP night	0.60	0.40	0.00 (3*)	1.00	0.60	0.28	

Conclusions: We found strong genetic effect on pulse pressure derived from ambulatory blood pressure monitoring.

2568 Behaviour of sympathetic nerve traffic and baroreflex function in dipper and non-dipper essential hypertensives

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Objective: Recent studies have prompted the hypothesis that neuroadrenergic and reflex mechanisms contribute to the occurrence of the "non-dipping" phoenomenon. These results, however, 1) were collected by employing indirect approaches to assess adrenergic function and 2) were based on a single (and thus poorly reproducible) assessment of the nocturnal blood pressure (BP) fall. Design and Methods: In 39 untreated lean essential hypertensives (age 51.9±1.1 yrs, mean±SEM) undergoing repeated 24 h BP monitorings in 2 non consecutive days (Spacelab 90207), we measured beat-to-beat systolic (S) and diastolic (D) BP (Finapres), heart rate (HR, EKG), plasma norepinephrine (NE, HPLC) and efferent postganglionic muscle sympathetic nerve traffic (MSNA, microneurography) at rest and during arterial baroreceptor manipulation via the vasoactive drugs infusion technique. 26 of the original 39 patients displayed reproducible nocturnal BP profile in the 2 monitoring periods and were classified as dippers (D, n=18, 50.8±1.6 yrs) or non-dippers (ND, n=8, 53.1±2.3 yrs) according to the magnitude of nocturnal BP fall > or < 10% of diurnal values.
Results: D and ND had similar 24h SBP (143.5±2.3 vs 145.7±2.8 mmHg), 24h DBP (87.9±1.9 vs 89.6±2.9 mmHg) and 24h HR (74.5±1.8 vs 71.9±2.6 b/min), while nocturnal DBP was less in D than in ND (77.8±2.0 vs 85.5±3 mmHg, $p<0.03$). NE levels were similar in the two groups (308±23 vs 321±35 pg/ml). This was also the case for MSNA values (63.0±3.8 vs 67.9±4.9 bs/100hb). Furthermore, HR and MSNA baroreflex responses were superimposable in D and ND. In the group as a whole, MSNA was significantly and directly related to both HR ($r=0.40, p<0.05$) and NE values ($r=0.44, p<0.03$).
Conclusions: Thus, the magnitude of sympathetic activation and the sensitivity of baroreflex control of both vagal and sympathetic outflows are similar in D and in ND. These data are therefore against the hypothesis that the "non dipping" phoenomenon depends on neuroadrenergic or baroreflex alterations.

2569 The real blood pressure load in smokers is not reflected by office blood pressure

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Although the acute effect of smoking is a rise in blood pressure(BP)and heart rate, several epidemiologic studies show that smokers tend to have a slightly lower BP than non-smokers. To test the hypothesis that smoking is associated with a rise in ambulatory BP, we examined the 24 h ambulatory BP in hypertensive smokers and hypertensive non-smokers. From February 2000 to October 2001 we performed 24 h ambulatory BP consecutively in treated or non treated hypertensive smokers (n=122) and hypertensive non-smokers (n=315) referred to our out-patient clinic. There were no differences in age, gender and Body Mass Index between the smoking group and the non-smoking group. The smokers were divided into heavy smokers (> 10 cigarettes per day) and light smokers. No differences were seen in office BP between heavy smokers and non-smokers (148.7 +19.6/92.4+12.7 mmHg vs. 149.7+20.7/91.2+11.6 mmHg). However, we found a significantly higher day-time systolic and diastolic BP in heavy smokers compared to non-smokers (147.5+15.6/90.8+10.1 mmHg vs. 142.5+14.6/87.5+11.0 mmHg). The well known tendency of day-time BP being lower than office BP was seen in all groups, but it was significantly less pronounced in heavy smokers, meaning that the day-time BP tends to be higher. Differences between office BP and day-time BP for heavy smokers were 1.0+12.1/1.6+8.0 mmHg and for non-smokers 7.3+13.9/3.8+9.3 mmHg ($p<0.05$). No significant difference were found for light smokers. We did not observe differences between the groups concerning office BP and night-time BP. In heavy smokers the office BP did not reflect the real BP load, meaning that the patients tended to be undertreated looking only at the office BP. As a consequence we routinely recommend 24 h ambulatory BP measurement in heavy smokers, at least before accepting the patient as well-treated on the basis of office BP alone.

2570 Lowering of ambulatory and daytime (but not clinic and nighttime) blood pressure by statin treatment

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A BP lowering effect of statins has been described by several authors but denied by others. Since only clinic BP was measured in most studies on this topic, we examined the BP effects of statins by 24-hour ambulatory BP monitoring (ABPM) which, compared to the clinic BP approach, i) provides a more reliable overall BP assessment and ii) allows the circadian BP profile to be tracked. We also addressed a further controversial issue, i.e. whether or not the putative BP lowering parallels the statin-induced lipid-lowering.
Outpatients referred to for hypertension or coronary artery disease, previously never treated with statins and having total serum cholesterol (TC) >5.17 mmol l^{-1} (200 mg dl^{-1}), were consecutively enrolled and randomized to a 2 month-treatment course of a statin (n=44, drug selection by clinic doctor: simvastatin or pravastatin, 10-40 mg daily; atorvastatin, 5-20 mg daily; cerivastatin, 0.2-0.4 mg daily) or of a control agent (Ctrl, n=18, soja lecitine 20 g daily). Any ongoing drug regimens were kept unchanged throughout. Pre- and post-treatment measurements included blood chemistry as well as clinic, 24-h, daytime (8am-22pm) and nighttime (24pm-6am) BP. Patients assigned to statin treatment were analyzed both as an overall group and as two subgroups identified as "stronger" or "weaker" responders according to the magnitude of the reduction in TC, the pre-defined, arbitrary cutoff being 1.3 mmol l^{-1} (50 mg dl^{-1}).
In the whole statin group, post- vs pre-treatment changes were -1.53±0.1 (mean±SEM) from 6.8±0.1 mmol l^{-1} for TC ($p<0.01$), -3.7±2.6 from 144±3 mmHg for clinic BP (p=ns, data refer to systolic), -3.7±1.0 from 130±2 mmHg for 24-h BP ($p<0.01$), -4.3±1.1 from 133±2 mmHg for daytime BP ($p<0.01$) and -1.4±1.2 from 120±2 mmHg for nighttime BP (p=ns). No significant lipid or BP changes were observed in the Ctrl group. In the "stronger" statin subgroup, the drop in TC was 1.87±0.1 mmol l^{-1} (n=27, $p<0.01$) and the BP changes were -8.5±2.6, -4.5±1.4 and -5.0±1.3, (all $p<0.01$) for the clinic, 24-hour and daytime values but -2.0±1.3 (p=ns) for the nighttime values, whereas in the "weaker" statin subgroup the drop in TC was 0.98±0.1 mmol l^{-1} (n=17, $p<0.01$) but no consistent change in any of the measured BPs was observed.
Our study indicates that statins do exert a mild-to-moderate BP lowering effect that: i) is consistently observed using an ABPM but not a clinic BP assessment, ii) is clearcut during the daytime but not the nightime, and iii) is more pronounced when there is a concomitant pronounced lowering of TC.

ENDOTHELIAL DYSFUNCTION: NEW TARGETS?

2571 The PPAR-gamma agonist rosiglitazone reduces endothelial activation in non-diabetic coronary artery disease patients

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Background: Endothelial cell activation is a key event in atherogenesis and atherosclerotic disease progression. Rosiglitazone, a Peroxisome Proliferator-Activated Receptor-gamma (PPAR-gamma) agonist, is an insulin-sensitising agent and is used in the treatment of type 2 diabetes mellitus. Recent experiments suggest that PPAR-gamma agonists directly modulate inflammatory processes within the vessel wall and may therefore inhibit endothelial activation. The aim of this study was to assess the effect of rosiglitazone on markers of endothelial activation in non-diabetic coronary artery disease patients.
Methods: We studied ninety-two patients (mean age 62 years, 78 males & 14 females) with stable angina and angiographically documented coronary artery disease. None of the patients had diabetes mellitus. Maintaining their current therapies, patients were randomised in a double-blind manner to placebo (n=46) or rosiglitazone (n=46, 4 mg/day for 8 weeks followed by 8mg/day for 4 weeks) for 12 weeks. Plasma levels of E-selectin and von Willebrand factor (vWF), markers of endothelial cell activation, were measured by enzyme-linked immunosorbent assay at baseline and at study end. Fasting insulin, glucose and lipid profile were also measured. The homeostasis model of insulin resistance index (HOMA-R) was calculated as a measure of insulin resistance. Results are shown as mean ± SD. One way ANOVA for repeated measurement was used to assess the effect of treatment on measured parameters.
Results: Eighty-four subjects completed the study. The levels of E-selectin and vWF were significantly reduced by rosiglitazone treatment compared with placebo. In the rosiglitazone group E-selectin decreased from 49 ± 16 to 43 ± 16 ng/mL (P=0.03) while vWF decreased from 139 ± 47 to 131 ± 44 IU/dl (P=0.01). Rosiglitazone treatment also significantly reduced insulin resistance (HOMA-R) compared to placebo (P = 0.02). However, significant increases in both LDL (2.63 ± 0.71 to 2.93 ± 0.71 mmol/L, P=0.01) and triglyceride levels (1.22 ± 0.62 to 1.47 ± 0.71 mmol/L, P=0.005) were observed in the rosiglitazone group compared to placebo. There was no treatment effect on HDL or fasting glucose levels. No significant correlation was noted between change in endothelial markers and change in HOMA-R.
Conclusions: We have shown for the first time that rosiglitazone significantly reduces endothelial cell activation in coronary artery disease patients without diabetes mellitus. This effect appears to be independent of other effects on lipid and glucose metabolism, suggesting a direct action on the vessel wall.

2572 Raloxifene reduces oxidative stress and improves endothelial dysfunction in spontaneously hypertensive rats

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Selective estrogen receptor modulators (SERM) such as raloxifene have beneficial estrogenic effects on lipids and bones without increasing the risk of breast or endometrial cancer. To investigate whether SERM exert vasoprotective effects similar to estrogens, male spontaneously hypertensive rats (SHR) were treated for 10 weeks with raloxifene (ralox) (10 mg/kg/d) or vehicle.

Methods and Results: Ralox improved endothelium-dependent vasodilatation of isolated aortic segments but did not affect endothelium-independent vasorelaxation or phenyleprine-induced vasoconstriction. Ralox treatment increased the release of NO from the vessel wall (NO electrode measurements) by enhanced expression and activity of endothelial NO synthase (eNOS) (arginine-citrulline conversion assays, RT-PCR). The vascular production of reactive oxygen species (ROS) was decreased by ralox (lucigenin chemiluminescence assays). Ralox did not alter the vascular expression of the NAD(P)H oxidase subunits p22phox and nox1 (RT-PCR), but reduced the activity and expression of vascular membrane-bound rac1, a GTPase required for the activation of the NAD(P)H oxidase (Western Blot, GTP-binding assays). Blood pressure reduction after bradykinin infusion was increased in ralox-treated SHR. Finally, systolic blood pressure was significantly decreased in SHR treated with ralox (tail-cuff method). All SERM effects were also detected in healthy, age-matched Wistar rats. In cultured rat aortic vascular smooth muscle cells, ralox inhibited angiotensin II-induced ROS production dependent on estrogen receptor activation (DCF fluorescence lasermicroscopy).

Conclusions: Raloxifene improves hypertension-induced endothelial dysfunction by increased bioavailability of NO. This is mediated by enhanced eNOS activity and reduced release of ROS from vascular cells. These vascular effects lead to blood pressure reduction and decreased vascular damage in male SHR.

2573 Impaired NOS pathway in diabetes mellitus: role of ADMA and DDAH

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Background: An endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine (ADMA) is elevated in patients with type 2 diabetic mellitus (DM). The mechanism by which ADMA becomes elevated is unclear. We determined if elevated glucose increases ADMA by impairing the activity of dimethylarginine dimethylaminohydrolase (DDAH), which metabolizes ADMA to citrulline. We further investigated the role of oxidative stress in glucose-induced ADMA elevation.

Methods and Results: Male Sprague-Dawley rats were fed normal chow or high-fat diet (n=5 each) with moderate streptozotocin injection to induce type 2 DM. The diabetic rats showed substantially elevated plasma ADMA compared to normal rats (1.33±0.31 vs. 0.48±0.08mM; $p<0.05$). Aortic DDAH activity, but not expression, was significantly reduced in diabetic rats and negatively correlated with their plasma ADMA levels ($p<0.05$). In vitro studies of vascular smooth muscle cells and endothelial cells revealed that DDAH activity was significantly reduced in both cell types exposed to high glucose (25.5mM). Glucose dose-dependently elevated endothelial elaboration of ADMA, which could be reduced to baseline by the addition of the antioxidant PEG-SOD (22U/mL). To determine if elevated glucose impairs the nitric oxide pathway, cGMP production by endothelial cells was measured and found to be significantly less in cells exposed to high glucose than cells grown in normal level of glucose (5.5mM). Addition of PEG-SOD restored both cGMP production and DDAH activity.

Conclusions: Mediated by oxidative stress, DDAH impairment accounts for ADMA elevation in high glucose condition and leads to reduced nitric oxide synthesis. This observation represents a new insight into diabetes-induced endothelial dysfunction.

2574 The functional integrity of the endothelium modulates dendritic cell adhesion and transmigration

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Atherosclerosis is a chronic disease triggered by endothelial injury and sustained by inflammation. The role of dendritic cells (DCs) in this inflammatory response has not been addressed. DCs are critical for the cell-mediated arm of an immune response, and are known to initiate inflammatory immunity. A fundamental aspect of DCs function is their capacity to adhere and migrate through vascular endothelial cells (EC). The aim of the study was to investigate DC/EC interaction under pro-atherosclerotic conditions. Human DC precursors were negatively separated from PBMC by magnetic beads and cultured in GM-CSF and IL-4. Typical phenotype of immature and mature DC was assessed by FACS. Confluent primary human microvascular ECs were incubated with isolated immature and mature DCs. Functional adhesion and transmigration assays were performed and analyzed using confocal laser microscopy and a fluorescent plate reader. We discovered that DC adhesion and migration are modulated by changes in endothelial function. Specifically, the endogenous NOS inhibitor ADMA (1 and 10 uM) (but not the prostacyclin inhibitor indomethacin) significantly increased DC binding and transmigration (+73 and +109%; $p<0.001$). DC adhesion and transmigration was markedly increased after exposing endothelial cells to hypoxia, oxLDL and/or TNFa (73-600%; $p<0.01$). Strikingly, HMG-CoA reductase inhibition (0.5 uM atorvastatin) and L-Arginine significantly decreased DC/EC interaction. The results of this study suggest that adhesion and migration of DCs is increased by stimuli known to accelerate atherogenesis. Vice versa, improvement of NOS activity inhibits DC adhesion. These findings may provide insight into the inflammatory processes occurring in atherosclerosis. As DCs control immunity, regulating DC/EC interaction may have relevance to inflammation and atherogenesis.

2575 Combined B-vitamin complexes and folate improve endothelial function in insulin-resistant hypertensive patients with microvascular disease

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Background: Microvascular involvement observed in patients with arterial hypertension could be related to endothelial dysfunction. High homocysteine levels are associated with impaired peripheral endothelium-dependent vasodilation. Several studies suggest that folic acid or B vitamins supplementations decrease homocysteine levels and possibly reduce cardiovascular risk. A link between endothelial dysfunction and the metabolic alterations typical of the Insulin Resistance Syndrome (IRS) has been previously demonstrated. However, little is known about the impact of homocysteine decrease, regardless of its basal levels, on endothelial function and metabolic features of IRS.

Methods: Sixteen patients (age 67±2 yrs; BMI 27.6±0.7 kg/m^2) with essential hypertension, chest pain, positive exercise testing and normal coronary arteries, impaired fasting glucose according to American Diabetes Association classification, hyperinsulinaemia and hypertriglyceridaemia were studied. A double blind randomised one month cross-over study with folic acid (5mg/day) plus vitamin B1-B6-B12 (250 mg-250 mg-500μg/day) or placebo was performed. After the end of each period, basal, post-ischaemic and post-nitrate forearm blood flow was evaluated by venous occlusion plethysmography. Blood pressure measurements and blood sampling were also performed.

Results; Compared to placebo, folic acid plus vitamin B treatment significantly decreased homocysteine levels (10.9±0.8 vs 17.2±2.0 μmol/l: $p<0.01$), mean blood pressure (104±2 vs 111±3 mmHG; $p<0.05$) and forearm basal (37.9±2.4 vs 49.2±4.9U; $p<0.05$) and post-ischaemic vascular resistance (28.8±2.8 vs 37.1±2.7U; <0.05) while a significant increment in post-ischaemic forearm blood flow (4.00±0.28 vs 3.16±0.17 ml/100ml/min; $p<0.02$) was observed. On the other hand, no differences were found on endothelium-independent nitrate-mediated vasodilation. Interestingly, no changes in blood glucose, insulin, HOMA index and triglyceride levels were observed. No evaluation of tetrahydrobiopterin levels was carried out.

Conclusions: In hypertensive patients with microvascular involvement, folic acid plus vitamin B supplementations improve endothelium-dependent vasodilation independently from modification of the main features of IRS. Homocysteine reduction may account for this improvement.

2576 Structural markers of atherosclerosis and functional markers of endothelial dysfunction in patients with unstable coronary artery disease

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Intima-media thickness of the common carotid artery (IMT) and an impaired arterial dilation in response to reactive hyperemia ("flow-mediated" dilation, FMD) are considered markers of atherosclerosis and endothelial dysfunction, which are thought to play a major role in the pathogenesis of coronary artery disease (CAD). A significant correlation between IMT and FMD has been described in patients (pts) with stable CAD. To investigate if a similar relationship occurs in pts with unstable CAD, we compared 30 consecutive pts referred to our CCU for acute coronary syndrome (Group A: 20 males, 59.2±9.8 years, 20 with acute myocardial infarction and 10 with unstable angina Braunwald Class IIIB) and 72 outpatients with stable CAD and/or multiple cardiovascular risk factors (CRF) (Group B: 43 males, 55.9±13.1 years, 22 with stable CAD and 50 with 2 or more CRF). For each patient we collected: 1) a cardiovascular risk score based upon several CFRs, previously validated in the SMART study (SMART#) 2) an high resolution US scan evaluation (linear array probe, 12-5MHz) of the common carotid artery IMT and of the percentage change of radial artery diameter in response to reactive hyperemia (FMD) induced by 5 min forearm stop-flow (brachial pneumatic tourniquet). At the moment of the US evaluation pts were fasting (12h) and in wash out from nitrates and calcium-antagonists (48h). Pts with acute CAD were evaluated from 4 to 6 days after the last spontaneous episode of transient myocardial ischemia. Sex prevalence and mean age of the 2 groups were not significantly different. Group A SMART# were slightly higher than Group B (7.70±1.39 vs 6.08±2.50, p=0.001). IMT (0.82±0.25 vs 0.76±0.19 mm, p NS) and FMD (9.01±5.57% vs 9.95±5.85%, p NS) were similar in the 2 groups. FMD was significantly correlated to IMT in Group B (R= -0.32, p=0.006) but not in Group A (R= -0.09, p NS). Finally, in Group B SMART# was strongly correlated to IMT (R= 0.79, p<0.0001) and FMD (R= -0.44, p<0.0001), whereas in Group A these correlations were weaker (SMART# vs IMT: R= 0.61, p=0.004, SMART# vs FMD: R= -0.29, p NS). In conclusion, this study confirms that IMT and FMD are correlated in pts with stable CAD. Similar findings were not observed in the population with unstable CAD studied. Moreover structural and functional markers of vascular disease correlated closely to SMART# in pts with stable CAD, but this was not the case for pts with unstable CAD. These intriguing finding, probably due to the multifactorial pathogenesis of the acute coronary syndromes and the eterogeneity of the pts studied, deserves further study.

THE "ACTIVE" PLATELET

2577 The RNA-binding protein TIA-R is involved p38 MAP-kinase-dependent protein synthesis in activated human platelets

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Platelets respond to thrombin or exposed subendothelial matrix at sites of vascular injury by forming hemostatic aggregates that prevent or limit bleeding. Although their hemostatic actions are of paramount importance, platelets also promote the development or progression of atherosclerosis or restenosis after angioplasty. It is generally believed, that these pathophysiologic functions depend largely on the release of preformed mediators. Here, we demonstrate that platelets may also contribute to prolonged inflammatory events by protein synthesis that is regulated by p38 MAP kinase. Among these proteins we further investigated the expression of Interleukin-1beta (IL-1b). Using gene array analysis we found in a previous study that platelets contained numerous megakaryocyte-derived mRNAs. Here, we demonstrated by 35S-methionine-uptake, that platelets translate mRNAs into protein in an activation-dependent fashion, a response that is abrogated when platelets were treated with the p38 MAP-kinase inhibitor SB203580. Following stimulation with PAF [10nM] or thrombin [0.1 U/ml] the IL-1b precursor mRNA was translated into protein (unstimulated control (co): 23±11 pg/ml; PAF [10-7M, 8hrs]: 2374±259pg/ml; thrombin [0.01U/ml, 8 hrs]: 615±120 pg/ml; p<0.05 vs. co). The IL-1b precursor protein was further processed and secreted as active, mature IL-1b. SB 203580 inhibited expression of both forms of IL-1b indicating, that p38 MAP kinase prevented synthesis, not conversion of the IL-1b precursor into the active cytokine. We found that the p38 MAP-kinase was phosphorylated within minutes and remained phosphorylated up to several hours. We then extracted the mRNA binding proteins of activated platelets that were treated with SB203580 or not and separated these by 2-dimensional gel electrophoreses. Among several proteins bound to platelet mRNA, we found that two proteins were bound to the mRNA only when the cells were treated with SB203580. By western blot analysis with a specific antibody, we identified one of these proteins as TIA-R. In conclusion, this study provides evidence that platelets synthesize IL-1b in an p38MAPkinase dependent fashion and that p38 MAP kinase recruits TIA-R to the platelet mRNA to inhibit translation. Regulated protein synthesis in activated platelets may be a mechanism by which platelets can enhance inflammatory outcomes and SB203580 might be a pharmacological approach to influence platelet-induced inflammation in a beneficial way.

2578 Increase in the number of fibrinogen receptors by glycoprotein IIb/IIIa inhibitors

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Purpose: Glycoprotein (GP)IIb/IIIa receptor blockade reduces the risk of thromboembolic episodes during percutaneous coronary interventions. Currently three intravenous agents are available: abciximab, eptifibatide and tirofiban. An upregulation of GPIIb/IIIa receptors during treatment with abciximab has been reported both in vivo and in vitro. The aim of this study was to investigate whether eptifibatide and tirofiban have the same effect on platelets.
Methods: After obtaining informed consent, blood from 6 healthy male volunteers (mean age ± SD: 42 ± 8) was drawn. Citrated whole blood was incubated with abciximab in concentrations 0, 1, 2, 3 and 4 μg/ml, epifibatide in concentrations 0, 0.1, 0.5, 1 μg/ml and tirofiban in concentrations 0, 10, 20, 50 and 100 ng/ml, based on previous pharmacokinetic studies of patients receiving recommended doses of each drug. For evaluation of platelet inhibition and number of GPIIb/IIIa receptors, platelets were labeled with FITC-conjugated antibodies against fibrinogen and CD41 (clone SZ22, non-fibrinogen ligand of GPIIb/IIIa receptor), and analyzed by flow cytometry. Mean fluorescence intensities at baseline and at mentioned concentrations were compared using Friedmann Repeated Measures ANOVA test.
Results: Inhibition of platelet fibrinogen binding of >80% was achieved with 2 μg/ml abciximab, 0.5 μg/ml eptifibatide and 50 ng/ml tirofiban. At these concentrations, the mean number of GPIIb/IIIa receptors increased 37 ± 13% (mean ± SD, p<0.01) for abciximab, 10 ± 3.4% (ns) for eptifibatide, and 36 ± 10% for tirofiban (p<0.05) compared to baseline.
Conclusion: While all three GPIIb/IIIa agents inhibit platelet fibrinogen binding effectively at the recommended doses, they have the capability of increasing the number of fibrinogen receptors on platelets in vitro. We have demonstrated for the first time an increase in the number of fibrinogen receptors induced by tirofiban. An increase in the number of receptors may be one of the mechanisms of post-procedural coronary adverse events despite GPIIb/IIIa inhibition. Clinical relevance of this phenomenon requires further investigation.

2579 The central role of platelet activation in determining the mode of presentation of acute coronary syndromes

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Background: Clinical studies have shown that in acute coronary syndromes, pretreatment with aspirin favours presentation with unstable angina (UA), while cigarette smoking favours presentation with myocardial infarction (AMI). Although serum markers of platelet activation are increased in patients with acute coronary syndromes but it is not known whether there is different activation in unstable angina and acute myocardial infarction.
Hypothesis: Platelet activation at the time of plaque rupture is a major determinant of the mode of presentation of acute coronary syndromes.
Methods: Patients presenting to the emergency room with acute myocardial infarction and unstable angina were recruited. Blood samples were analysed within 4 hours, for mean platelet component (MPC), a measure of platelet activation derived from flow cytometry utilising a laser source and light scattering technology. MPC reflects the granularity of platelets and is inversely related to the expression of CD62P.
Results: The study group comprised 25 patients with AMI and 64 with UA. The groups were similar as regards age and gender distribution. Mean platelet component was lower in AMI than UA (24.67±1.58 v. 25.86±1.38 g/dl, p=0.001), reflecting significantly greater platelet activation. This difference persisted when the unstable angina cohort was limited to 48 patients at high risk of future cardiac events defined by troponin I concentration >0.1μg/l, or ischaemic ST/T changes on the presenting ECG (24.67±1.58 versus 25.81±1.44 g/dl, p=0.016). Pretreatment with aspirin was less frequent (16.0% versus 68.8%, p<0.0001), and smoking more frequent (48.0% versus 28.1%, p=0.08) in AMI than UA, but in multivariate analysis mean platelet component (odds ratio 0.36; 95% confidence intervals 0.18-0.72) was retained as an independent predictor of diagnosis, despite adjustment aspirin treatment and smoking. Mean platelet volume tended to be higher in AMI than UA (9.4±1.2 versus 9.1±0.9 fl), but the difference was not significant.
Conclusion: This study has shown diagnosis-specific differences in platelet activation in acute coronary syndromes. The finding that platelet activation at the time of presentation was greater in acute myocardial infarction than unstable angina confirms the central role of thrombogenicity in determining the clinical expression of plaque events.

2580 Baseline platelet function in "low responders" to antiplatelet treatment following coronary stent implantation

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Although most pts undergoing coronary stent implantation (STI) routinely receive double antiplatelet treatment, aspirin plus clopidogrel, a thrombotic risk early after STI still persists. We compared baseline platelet activation and aggregation among pts with low and high inhibition of platelet aggregation (PA) following STI. Methods: PA was assessed before and 24 hrs after STI in 31 consecutive pts using a light transmittance aggregometry after stimuli with 6μM of ADP and 6μg/mL of collagen. GP IIb/IIIa (anti-fibrinogen-FITC) and P-selectin (CD62-PE) platelet surface expression was also measured after stimuli with 2μM of ADP before and 24 hrs after STI using whole blood flow cytometry. All pts were treated with aspirin (100 mg/day) and received a 300 mg loading-dose of clopidogrel at intervention time. During intervention 100 IU/kg of heparin was administered. Pts receiving GP IIb/IIIa inhibitors were excluded. According to the grade of PA upon 6μM ADP stimuli 24 hrs after STI, pts were divided into two groups: G1 (PA>30%) and G2 (PA<30%). Cut-off value of 30% was the median value of our study population and it is a widely used cut-off clinical value to assess platelet inhibition. Time point of 24 hrs is crucial for early coronary thrombosis and at this time full effect of loading-dose of clopidogrel should be observed. Results (mean±SD): G1 and G2 were composed of 13 (10 men;age:63±7y) and 18 (17 men;age:62±11y) pts, respectively. PA upon ADP stimuli 24 hrs after STI was 52,92±16,8% in G1 and 18,67±7,6% in G2 ($p<0.001$). G1 presented a greater PA than G2 even upon stimuli with collagen 24 hrs after STI (55,05±26,34% vs 35,88±20,91%; p=0.032). No differences in baseline PA with ADP (54,76±24% vs 44,91±11,24%; p=0.19) or with collagen (47,10±16,83% vs 42,39±16,32%; p=0.44) were observed between G1 and G2. Therefore, despite antiplatelet treatment, 13 out of 31 (42%) pts had low inhibition of PA 24 hrs after STI. P-selectin expression was 44%±16% vs 42%±19% (P=0.8) at baseline and 27±13% vs 22±15% (p=0.4) 24 hours after STI in G1 and G2, respectively. GP IIb/IIIa expression was 68%±19% vs 51%±23% (p=0.040) at baseline and 57±25% vs 35±29% (p=0.048) 24 hrs after STI. Conclusion: Despite aspirin and clopidogrel treatment, a high proportion of pts undergoing STI may have a poor inhibition of PA early after the intervention. An enhanced GP IIb/IIIa receptor activation at baseline in these pts may help to identify candidates who may obtain the largest benefit from treatment with GP IIb/IIIa receptor antagonists.

2581 The adverse effects of COX-2 inhibitors on cardiovascular disease: fact or fiction

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Background: At the turn of the new millennium, a new class of anti-inflammatory agents associated with minimal gastric toxicity were introduced, termed the COX-2 inhibitors. A recent subgroup analysis of two randomized trials assessing the efficacy of COX-2 inhibitors suggested that the effects of these agents on prostacyclin synthesis may adversely increase prothrombotic activity, increasing the risk of cardiovascular events. However, no literature to date addresses the safety of COX-2 inhibitors in a specific cardiovascular patient population.

Objective: We examined outcomes in individuals who had previously been taking COX-2 inhibitors and were admitted with an acute coronary syndrome, either unstable angina (UA) or myocardial infarction (MI).

Methods: We utilized a prospective registry-based disease management database, Improving Cardiovascular Outcomes in Nova Scotia (ICONS), to identify all individuals in Nova Scotia, Canada with a discharge diagnosis of acute coronary syndrome (ACS) between January 1, 1999 and December 31, 2000. We identified a cohort of 302 individuals on COX-2 inhibitors and compared them to the total 6829 patients admitted with acute coronary syndrome. Outcome measures including length of hospital stay, in hospital death rate, readmission rates for acute coronary syndrome (ACS) at one year, and one year mortality rates were compared amongst both groups.

Results: The relative percentage of patients on COX-2 inhibitors was 4.4% of a total of 6829 individuals admitted with an acute coronary syndrome between 1999-2000. The mean length of hospital stay was 9.64 days for the total population versus 10.06 days for the COX-2 patients (p=NS). The in hospital mortality rate was identical in both groups at 8.3% (p=NS). Although readmission rates within one year were similar for the COX-2 inhibitor population and the total population at 32.9% and 29.7% respectively (p=NS), patients on the anti-inflammatory medications were more likely to be readmitted with unstable angina within the year, 24.9% vs 17.9% ($p<0.05$). Finally, one year mortality was not statistically higher for those individuals on COX-2 inhibitors.

Conclusion: These findings are particularly pertinent in light of the recent debate of whether COX-2 inhibitors are truly deleterious for those individuals with underlying ischemic heart disease. Although limited, our findings would suggest that these novel anti-inflammatory agents may not increase the risk of an adverse cardiovascular outcome.

2582 Acute resolution of hyperglycemia normalizes platelet responsiveness to nitric oxide in diabetics with acute coronary syndromes

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Background: Diabetics mellitus (DM) is associated with increased mortality in acute coronary syndromes (ACS) when compared with non- DM subjects. The DIGAMI study in DM patients with acute myocardial infarction (AMI) demonstrated that reversal of hyperglycaemia is associated with reductions in 1 year mortality, but no mechanism(s) have been demonstrated for this effect. We now tested the null hypothesis that platelet responsiveness to the anti-aggregatory effects of nitric oxide (NO) donors are independent of BSL.

Methods: DM subjects with ACS (unstable angina or non-Q-wave AMI) and an admission BSL >10mmol/L were enrolled in the study. Subjects were randomized to intravenous (IV) or subcutaneous (SC) insulin administration. Platelet function was assessed by ADP-induced aggregation (Ohms) and its inhibition by the NO donor sodium nitroprusside (SNP, % inhibition of control). This was performed in whole blood and platelet rich plasma (PRP) via impedance aggregometry. Effects on whole blood superoxide (O2-) and platelet cyclic GMP (cGMP) response to SNP were also compared. Data were collected at baseline and after 12 hours of treatment.

Results 47 patients were randomized. Patients were 67±1.8 (SE)years old with an admission BSL of 16.8±1 and an HbA1c of 8.8±.3. On admission 24% of patients were insulin dependent. The effects of therapy in whole blood are shown in Table 1, expressed as change over 12 hrs (delta).There were no significant differences, between the treatment groups when performing the above experiments in PRP. Platelet cGMP response did not differ significantly between the two treatment groups.

delta(0-12hrs)	IV (n=24)	SC(n=23)	Significance
BSL (mmolo/L)	-11.1 ± 1.8	-3.7 ± 1.2	p<0.01
ADP response (Ohms)	0.5 ± 0.4	0.1 ± 0.8	
SNP Response (% inhibition)	15.4 ± 4.8	2.4 ± 3.6	p<0.05
O2- content (mv)	-12.5 ± 5.5	5.7 ± 3.5	p<0.05

Conclusions: In DM patients presenting with an ACS, more aggressive BSL control with IV insulin significantly enhances the antiaggregatory effects of NO when compared to SC insulin. The 'scavenging' of NO by O2-, rather than stabilization of soluble guanylate cyclase, probably contributes to these findings.

ADVANCES IN HYPERTENSION MANAGEMENT

2593 Sildenafil (Viagra®) improves arterial stiffness in hypertensive patients

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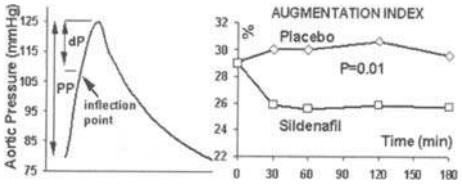
Background: Sildenafil (Viagra®) is a new, effective drug for erectile dysfunction acting on the metabolism of nitric oxide. However, its effects on the cardiovascular system have not been thoroughly investigated. Wave reflection along the arterial tree is an important index of arterial stiffening and cardiac afterload and has been inversely associated with exercise capacity.
Methods: To investigate the effect of sildenafil on arterial wave reflection we studied 17 hypertensive patients (age 72±7 years) in a randomized, double-blind, cross-over fashion (50 mg of sildenafil and placebo). Wave reflection was studied using a validated system (Sphygmocor®) that employs (i) high-fidelity arterial tonometry (Millar tonometer) for the non-invasive registration of radial pulse waveform and (ii) appropriate computer software for pulse wave analysis. Aortic pressure waveform was synthesized from the radial waveform using a generalized transfer function. Augmentation index (=dP/PP %, fig.: waveform) was measured as an index of wave reflection. Inflection point (Pi) was defined with mathematical algorithms. Lower values of augmentation index indicate reduced arterial stiffening and reduced cardiac load and vice-versa.
Results: Sildenafil caused a decrease in aortic systolic and diastolic pressure (by 16.2 and 10.1 mmHg respectively; P<.001 for both). Sildenafil led to a significant decrease in augmentation index indicating decreased effect of wave reflection from the periphery (fig.: trends).



Viagra and wave reflection.

Conclusions: Sildenafil leads to a decrease of wave reflection in hypertensive patients. This finding has important implications for arterial stiffening and the pulsatile load of the heart and may contribute to improved exercise capacity of the patients at intercourse.

2594 Different effects of amlodipine and valsartan on renal haemodynamics in essential hypertension

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Objective: Angiotensin AT1-receptor blockers have been found to be renoprotective in hypertensive patients with nephropathy. To elucidate the renoprotective mechanism of AT1-receptor blockers, we compared the effects of the AT1-receptor blocker valsartan with that of the calcium channel blocker amlodipine on renal hemodynamics and microcirculation. **Methods:** Fifty-eight patients (age, 50.2±9.0 years) with mild to moderate essential hypertension were included in a randomized, double-blind study to receive either valsartan (80-160 mg) or amlodipine (5-10 mg). Renal plasma flow (RPF) and glomerular filtration rate (GFR) were measured before and after 8 weeks of treatment. Infusion of NG-monomethyl-L-arginine (L-NMMA; 4.25 mg/kg) was used to assess the contribution of nitric oxide to the perfusion of the renal vasculature. Glomerular hydrostatic pressure (PGlo) and resistances of the afferent (RA) and efferent (RE) arterioles were calculated according to Gomez' formulae. **Results:** Blood pressure control was similar in both groups. RPF did not change with either treatment. In contrast, GFR increased with amlodipine (+8±14 mL/min; p<0.01), but was preserved with valsartan (-0.3±11.3 mL/min; p=n.s.; p<0.05 for comparison between amlodipine and valsartan). Treatment with amlodipine caused a more marked increase in the RE/RA ratio than the one with valsartan (+0.26±0.26 vs. +0.13±0.24, p<0.05) which was paralleled by an increase in PGlo in amlodipine (+1.9±4.3 mmHg; p<0.05) but not in valsartan treated patients (-0.4±4.3 mmHg; p=n.s.). Valsartan maintained the response of RPF to L-NMMA (-44±60 vs. -40±56 mL/min before and after treatment, respectively; p=n.s.), whereas the response of RPF to L-NMMA was reduced with amlodipine treatment (-58±67 vs. -22±55 mL/min, respectively; p<0.05). **Conclusion:** At similar blood pressure control, GFR and PGlo were maintained with valsartan treatment whereas amlodipine leads to glomerular hyperfiltration paralleled by an increase in PGlo. The effects on nitric oxide bioavailability in the renal vasculature contrast between valsartan and amlodipine, too. Both results might account for the favorable renal outcome in patients treated with AT1-receptor blockers.

2595 Chronic angiotensin II receptor blockade reduces sympathetic nerve traffic and improves insulin resistance in obese hypertensives

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Objective: Animal studies have suggested that angiotensin II (AII) may exert in obese subjects pro-hypertensive effects by activating sympathetic drive and thus promoting, by adrenergic mechanisms, the occurrence of an insulin-resistance (IR) state. The present study was aimed at testing this hypothesis by examining the effects of chronic AII receptor blockade on muscle sympathetic outflow as well as on insulin sensitivity in obesity-related hypertension.
Design and Methods: In 24 obeses with a mild to moderate essential hypertension (age: 50.3±1.8 yrs, body mass index: 34.3±0.9 kg/m^2, mean arterial pressure, MAP: 111.4±2.0 mmHg, mean±SEM) we measured 24 h ambulatory, clinic and beat-to-beat MAP along with heart rate (HR, EKG) values. Measurements, which also included direct microneurographic assessment of muscle sympathetic nerve traffic (MSNA) as well as evaluation of the IR index (oral glucose overload test), were performed in the no-drug placebo condition and repeated following 12 weeks of either candesartan cilexetil (C, 8/16 mg o.d.) or hydrochlorothiazide (H, 25/50 mg o.d.) daily oral administration, accordingly to a double blind, randomized two parallel groups study design.
Results: Baseline hemodynamic, metabolic and neuroadrenergic values were similar in the two groups. C caused a significant MAP reduction (from 112.5±3.4 to 90.1±3.0 mmHg, p<0.01) coupled with a significant MSNA decrease (from 68.5±3.4 to 55.9±3.2 bs/100 hb, p<0.01) and an improved insulin sensitivity (+24.5±5.1, p<0.05). In contrast, for MAP reductions similar to C (from 110.5±3.2 to 93.1±2.9 mmHg, p<0.01), H did not significantly affect either MSNA (from 68.8±3.5 to 69.6±3.4 bs/100 hb) or insulin sensitivity (-8.7±6.1%).
Conclusions: These data provide direct evidence that renin-angiotensin system partecipates at the sympathoexcitation and at the IR state which characterize obesity-related hypertension. They also show that, at variance from diuretics, A II receptor blockers are capable to exert sympathoinhibitory effects coupled with improved metabolic insulin profile.

2596 Effects of antihypertensive treatment on cardiac and vascular remodelling in older hypertensives: the ICARe Dicomano study

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Background: Hypertension is one of the major cardiac and cerebrovascular risk factors. Although there is general consensus on the efficacy of antihypertensive treatment, hypertension is often underdiagnosed and undertreated in older subjects. The aim of the present study is to compare cardiac and vascular changes in treated and untreated older hypertensive subjects.
Methods: Community-dwelling individuals aged >=65 years living in Dicomano, a small town in Italy, underwent extensive clinical examination, echocardiography, carotid ultrasonography and applanation tonometry. In the present analisys we included 225 untreated and 213 treated hypertensive subjects.
Results: Only 20% of the treated subjects had adequate control of blood pressure (<140/90 mmHg). Treated subjects were younger (73±6 vs. 74±7 yrs, p=.026) and had a higher prevalence of comorbidity (history of coronary and cerebrovascular disease: 14% vs. 4%, p<.0001, and 24% vs. 7%, p<.0001, respectively) than untreated subjects. Left ventricular wall thickness and mass index (LVMI) were similar in the two groups. Carotid intimal-medial thickness (IMT) and the number of carotid plaques (0.88±0.17 vs. 0.84±0.17 mm, p=.033, 3±2 vs. 2±2, p=.020) were greater, whereas carotid stiffness index (Beta) was lower (4.55±2.02 vs. 5.35±2.77, p=.003) in treated subjects. To reduce the confounding effect of the non homogeneous distribution of comorbidity in the study population, all subjects with history of cardiac and cerebrovascular diseases were excluded from the subsequent analyses; these subjects were divided into three groups by presence and adequacy of antihypertensive treatment (193 not treated=NT, 22 adequately treated=AT, 108 undertreated=UT). When compared with UT subjects, AT subjects showed significantly lower left ventricular mass and LVMI (131±43 vs. 168±61 g, p=.017 and 77±23 vs. 99±34 g/m^2, p=.008, respectively) while IMT, carotid diameter in diastole, and the number of carotid plaques were similar in the two groups. The stiffness index was significantly higher in the NT group compared with the UT group (5.38±2.88 vs. 4.41±1.84, p=.015).
Conclusions: In our older population, effective anti-hypertensive treatment is associated with a significant reduction in cardiac remodeling. Furthermore, although carotid structural parameters are similar, independent of the presence and efficacy of treatment, carotid artery stiffness is significantly reduced in treated subjects. This study suggests that, in older patients, an effective antihypertensive treatment may reduce the degree of cardiovascular remodeling.

2597 Cardiovascular morbidity in hypertensive patients treated with angiotensin-converting enzyme inhibitors or calcium channel blockers in primary care

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In hypertensive patients attending the Glasgow Blood Pressure Clinic, a secondary and tertiary referral centre, treatment with ACE inhibitors (ACEI) is associated with cardiovascular mortality lower than that following calcium channel blocker (CCB) treatment. The objective of this study was to compare cardiovascular morbidity in patients receiving these drug classes in the primary care setting. The United Kingdom General Practice Research Database (GPRD) contains validated demographic, diagnostic and prescription information on over 3 million patients in primary care. From these, we identified a priori a representative sample of 105,965 treated hypertensives eligible for a retrospective cohort analysis. Only those who received ACEI or CCB as first-line therapy and without evidence of cardiovascular disease prior to treatment with a drug of interest were included. Cardiovascular morbidity rates in ACEI and CCB were compared as relative hazard ratios (RHR) with 95% confidence intervals (CI) using Cox proportional hazard model with adjustment for age, gender and year of entry. The results are shown in the table.

Events	ACEI (n = 11249)	CCB (n = 12494)	RHR	95% CI
CHD (incl angina)	946 (8.4%)	1902 (15.2%)	0.63	0.58, 0.68
CHD (excl angina)	509 (4.5%)	1063 (8.5%)	0.91	0.82, 1.02
Cerebrovascular	498 (4.4%)	863 (6.9%)	0.87	0.78, 0.97
LV failure	598 (5.3%)	1009 (8.1%)	0.90	0.81, 1.00

Compared with CCB, first-line treatment of hypertension with ACEI was associated with highly significant reductions in cardiovascular morbidity - 37% for CHD and 13% for cerebrovascular events. Trends in favour of ACEI were seen for CHD even if symptomatic angina was excluded and for LV failure. Since approximately 25% of patients in each group went on to receive a drug from the other class of interest, the findings may underestimate the true difference. In the primary care setting, treatment of hypertension with ACEI is associated with lower cardiovascular morbidity than that following CCB. The results support earlier findings and suggest that observational studies in large well-documented, populations treated in the usual clinical setting may allow differentiation of the cardiovascular protective effects of antihypertensive drugs.

2598 Antihypertensive therapy at the onset of an acute myocardial infarction predicts in-hospital mortality

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Background: Clinical studies have shown that both conventional antihypertensive drugs (thiazide diuretics and beta-blockers) and the newer agents (calcium blockers and angiotensin-converting enzyme (ACE) inhibitors) are almost equally efficacious with regard to effects on blood pressure, and in preventing cardiovascular morbidity and mortality. However, the potential value of these drugs when hypertensive patients (pts) suffer an acute myocardial infarction (AMI) is not known. For practical reasons this issue can not be studied in a clinical trial. We applied an observational study design to investigate whether being on different antihypertensive drugs at the start of symptoms could influence in-hospital death in hypertensive AMI pts.
Methods: Of a total of 898 consecutive pts discharged dead or alive with the diagnosis of AMI (ICD 10 I21/I22), 299 pts reported a history of previous hypertension, and these were included in the study. 16 hospitals participated, and the sampling of pts was done during a three months period in 1999/2000. Variables were entered into a logistic regression model.
Results: The main predictors of death were age and the use of diuretics and calcium blockers, while the use of ACE inhibitors was associated with a significant 58% reduction in mortality (table). Other cardiovascular drugs (beta-blockers, aspirin, warfarin, digitalis) did not influence in-hospital death. Nor did gender, previous coronary heart disease, heart failure, diabetes mellitus nor smoking.

		Adjusted odds ratio	95% confidence interval	P value
Age (n = 299)	>70 years	3.26	1.29-8.24	0.012
Diuretics (n = 116)	yes/no	3.12	1.52-6.41	0.002
Calcium blockers (n = 105)	yes/no	2.26	1.14-4.48	0.020
ACE inhibitors (n = 104)	yes/no	0.42	0.19-0.93	0.033

Conclusions: The present observational study shows that being on ACE inhibitors at the start of symptoms reduced in-hospital death in hypertensive pts suffering an AMI, while diuretics and calcium blockers increased the risk for in-hospital death.

PROGRESS IN PREVENTION OF STROKE

2599 Biochemical composition and echostructure of carotid plaques from symptomatic and asymptomatic patients

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As carotid atherosclerotic plaques have been associated with cerebrovascular events, their early detection and characterization with ultrasonography has become more and more relevant. Echolucency, classically related to haemorrhage or lipid, has been associated with higher neurological risk. Nevertheless, the relation between symptoms, echostructure and plaque composition is not fully understood. In this study, biochemical components of carotid plaques were compared between symptomatic and asymptomatic patients, and echolucent and echorich plaques.
Thirty human carotid plaques were snap-frozen immediately after their removal by endarterectomy. Thirteen plaques were associated with ipsilateral hemispheric symptoms. Carotid high-definition ultrasonography (ATL-HDI3000) was performed preoperatively. Images were digitalized and standardized with computer-assisted analysis, being divided into two equal groups: predominantly echolucent or echorich. The total amounts of hydroxyapatite, collagen, elastin, soluble protein and DNA were determined.
Results (table) were normalized and expressed in μg/mg of plaque wet weight, except for hydroxyapatite, in mg/mg of plaque wet weight. Statistical analysis was done using unpaired Student's t-test.

	Symptomatic	Asymptomatic	p	Echolucent	Echorich	p
Hydroxyapatite	4,3±4,2	18,6±21,1	0,04	14,7±19,1	11,5±15,3	NS
Collagen	95,4±27,9	77,7±13,1	0,04	91,7±22,9	69,0±19,0	0,02
Elastin	22,8±6,2	17,6±5,6	0,03	22,1±5,6	16,9±3,6	0,01
Soluble Protein	8,9±2,3	7,0±1,5	0,01	8,1±2,2	7,7±2,3	NS
DNA	73,2±17,1	61,2±11,9	0,03	74,9±13,7	60,5±14,3	0,02

Table I – Normalized results (mean±SD) for plaque wet weight (hydroxyapatite, in mg/mg of plaque wet weight and the other variables in μg/mg of plaque wet weight). NS, not significant.

In conclusion, plaques associated with symptoms contained less hydroxyapatite, more collagen, elastin, soluble protein and DNA. Similar results were also obtained for the echolucent plaques. This study suggests that echogenicity is not necessarily associated with the presence of high levels of collagen and elastin.

2600 Association of gene-gene and gene-environment interactions in atrial fibrillation and sinus rhythm with cerebro-vascular events

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Background: Gene polymorphisms (PM), involved in hemostasis and blood pressure regulation have been inconsistently associated with cardiovascular disease either directly or through their association with blood levels of cardiovascular risk factors
Objective: Association of classical risk factors, PM of the renin-angiotensin-aldosteron-system: (angiotensinogen (ANG) 174, ANG 235, ACE insertion/deletion (ID)), and the hemostasis: (factor (F) VII 353, PAI-1 4G/5G), as well as their interactions with cerebro-vascular events (CVE), stratified by sinus rhythm (SR) and atrial fibrillation (AFIB).
Patients and Methods: 3316 patients [62±11 years, 70% male, 59% hypertension (HT), 32% diabetes mellitus (DM), 78% coronary artery disease, SR: n=2946, AFIB=370] of the Ludwigshafen Risk and Cardiovascular Health study. A CVE was defined as TIA, PRIND, or stroke in the medical history (Hx). A multiple regression model (PROC GLM of the SAS package) was used for interaction-analysis.
Results: All PM where in Hardy Weinberg equilibrium. No influence of CAD, gender, PAI-1, d-dimers, and the single PM ANG 174, ANG235, PAI-1 4G/5G on Hx of CVE were seen in both groups. In SR age, hypertension, diabetes mellitus (all $p<0.001$), and in AFIB ACE ID and FVIII353 were associated with a Hx of CVE (all $p<0.05$) (table).

Gene-gene/gene-environment interaction

	SR	AFIB
Hx of CVE, %	7%, n=219	13%, n=49
ANG 174/ FVIII353	<0.0001	n.s.
ANG 235/ FVIII353	<0.005	n.s.
ACE ID/DM	<0.05	n.s.
ACE ID/ANG 174	<0.05	n.s.
ACE ID/PAI4G5G	n.s.	<0.05
ANG235/D-dimer	n.s.	<0.05
PAI4G5G/HT	n.s.	<0.05

Conclusion: 1) Classical risk factors (DM, HT, Age) for a CVE were significant predictors in SR but not in AFIB. 2) Monogenetic influence of the ACE ID and FVII353 genotype in the prediction of a CVE were seen in AFIB. 3) Despite no influence as monogenetic factor, different patterns of gene-gene and gene-environmental interaction were associated with a Hx of CVE in SR vs. AFIB.

2601 The increase recognition of cardiac papillary fibroelastoma. A French multicenter study about 46 cases

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Papillary fibroelastoma (PF) are rare, small, benign tumors representing 10% of heart tumors, and the most common valvular tumor. Although they are detected more frequently since the advent of echocardiography and especially transesophageal echocardiography (TEE), there are no guidelines for their management.
This was a retrospective cohort study. Patients were collected from the data bases of the biggest cardiac centers in France (echocardiographic laboratory, surgical department).
The total study group consisted of 46 patients [(20 women, 26 men) mean age 54 ± 12 years] with typical echocardiographic criteria of PF, 35 patients underwent surgery with histologic confirmation. They were valvular tumor in 86% of the cases and intracardiac tumor in 13%. Neurologic events occurred in 81% of the patients and a few patients were asymptomatic. These small tumors were detected by TEE in all cases but TTE was negative in 63% of the cases. This study underlines the leading role of echocardiography and particularly TEE in the diagnosis of FE.
Due to the high risk of embolic events, it seems reasonable to perform surgical removal for left sided PE.

2602 Pregnancy-associated plasma protein: a new marker of carotid plaque vulnerability?

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Background: Pregnancy-associated plasma protein A (PAPP-A), a proatherosclerotic metalloproteinases, it has been recently recognized as a marker of plaque vulnerability in pts affected by acute coronary syndromes. Also in carotid district, plaque instability has been linked to onset of cerebrovascular events. However, little is known about PAPP-A expression in carotid atherosclerotic disease and if this protein can represent a marker of vulnerable plaque also in the carotid district. **Methods:** Twenty carotid plaques of pts (12 male and 8 female, 68±8 yo) who suffered from stroke formed the base of the study. Echographic and angiographic examination was performed in all cases. Immunohistochemical staining for PAPP-A, smooth muscle cells, CD68 (macrophages) and CD3 (T-lymphocytes) was performed on tissue samples after carotid endarterectomy and graded by semiquantitative analysis. Immunofluorescence confocal microscopy was utilized to confirm PAPP-A cell expression within the plaque. Carotid plaques were divided in four groups: 1) stable plaques (n=5, cap thickness >150 μ and inflammatory cells infiltrate in the cap (ICI) < 25 cells x HPF); 2) vulnerable plaques (n=5, cap thickness < 80 μ and ICI > 25 cells x HPF; 3) ruptured plaques with thrombus (n=5); 4) healed plaques with organized thrombus. **Results:** Angiographic stenosis was similar in all groups (between 65 and 85%). At immunohistochemestry, a strong positivity (+++) for PAPP-A was expressed by macrophage and T-lymphocyte cells in group 2 and 3 in correspondence of the cap, shoulder, and rupture site of the plaque, respectively. Low expression (+) was present in group 1 and 4 (p=.0001). Immunofluorescence confocal microscopy confirmed the expression of PAPP-A by inflammatory cells within the cap and shoulder of the plaque.
Conclusions: Our study suggest that PAPP-A may play a key role in carotid plaque destabilization and rupture. Further serologic studies are necessary to determine if PAPP-A can represents a new target for the prevention of atherosclerotic cerebrovascular disease.

2603 Novel device for percutaneous left atrial appendage transcatheter occlusion (PLAATO) to prevent stroke in patients with atrial fibrillation

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Background: Warfarin therapy has been shown to reduce the risk of stroke in patients (pts) with atrial fibrillation. However, it has a narrow therapeutic range and is contraindicated in many. The left atrial appendage is the source of thrombi in > 90%. Occlusion of the left atrial appendage may prevent cardioembolic complications. The purpose of this study was to evaluate the feasibility of the PLAATO in occluding the left atrial appendage. **Patients:** PLAATO was attempted in 17 pts aged between 59 - 78 yrs (mean 70 ± 6) with atrial fibrillation, additional stroke risk factors, and contraindication to warfarin. The left atrial appendage ostial diameter of these pts varied between 12 - 21 mm (mean 17 ± 4). **Methods:** PLAATO™ system consists of a self-expandable nitinol cage covered with a biocompatible membrane. It is delivered through a 12Fr transseptal catheter specially designed to access the left atrial appendage. Animal studies have shown efficacy at sealing the left atrial appendage with complete encapsulation and endothelialization by 1-3 months. The implant has not served as the nidus for new thrombus. Angiography is used to determine the initial device diameter. However, one can collapse the implant and either reposition or remove and replace it with a different size. **Results:** The procedure was successful in occluding the left atrial appendage in all patients. In one patient with a complex left atrial appendage anatomy a hemopericardium developed caused by catheter manipulation before implantation of the device. Pericardiocentesis was performed without sequelae. The procedure was successful in a second attempt for weeks later. There were 4 successful retrievals to change implant size. Devices with diameter of 18 (n=2), 23 (n=4), 26 (n=4), 29 (n=4) & 32 (n=3) mm were ultimately implanted without complications. Transesophageal echocardiography showed the device well seated. Follow up x-rays and echocardiograms revealed stable implants. No thrombi were detected, no complications occurred during follow-up (1-5 months).
Conclusions: (1) Transcatheter closure of the left atrial appendage is feasible; (2) this novel technology may offer an option for pts with AF who are not candidates for anticoagulation; (3) a clinical trial is warranted to show the long term safety and efficacy in reducing stroke.

2604 Rosuvastatin, a new HMG-CoA reductase inhibitor, up-regulates endothelial nitric oxide synthase and protects from stroke in mice

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Background and Objective: HMG-CoA reductase inhibitors (statins) are cholesterol-lowering drugs which reduce the risk of myocardial infarction and stroke. In this study we investigated whether rosuvastatin, a new and relatively hydrophilic HMG-CoA reductase inhibitor, up-regulates endothelial nitric oxide synthase (eNOS) expression and activity and protects from cerebral ischemia in mice.

Methods: Bovine aortic endothelial cells in culture were treated with rosuvastatin for 4 to 48 h and 129/SV mice were administered rosuvastatin s.c. for 10 days. The expression and activity of eNOS were determined by reverse-transcriptase polymerase chain reaction, Western blotting and arginine-citrulline assays. Cerebral ischemia was induced by occlusion of the middle cerebral artery for 2h followed by 22 h reperfusion after which stroke volume was determined.

Results: Treatment of endothelial cells with rosuvastatin up-regulated eNOS mRNA and protein expression in a concentration- and time-dependent manner. In aortas of 129/SV wild-type mice, treatment with 0.2, 2, and 20 mg/kg rosuvastatin significantly upregulated eNOS mRNA by 50%, 142%, and 205%. NOS activity was significantly increased by 75%, 145%, and 320%, respectively. Stroke volume after 2-hour middle cerebral artery occlusion was reduced by 27%, 56%, and 50% (at doses of 0.2, 2 and 20 mg kg-1, respectively). Serum cholesterol and triglyceride levels were not significantly lowered by the treatment.

Conclusions: The new HMG-CoA reductase inhibitor rosuvastatin dose-dependently up-regulates eNOS expression and activity in endothelial cells and protects from cerebral ischemia in mice. The effects are independent of changes in cholesterol levels. Reduction of stroke size by the relatively hydrophilic rosuvastatin was at least as effective as equal concentrations of the lipophilic simvastatin and atorvastatin in this animal model.

THE MANY FACETS OF VESSEL WALL MAINTAINANCY

2613 Paracrine recruitment of mesenchymal cells via VEGF-induced expression of PDGF-B in endothelial cells

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Introduction: The formation of capillaries (angiogenesis) and the growth of pre-existing collateral arteries (arteriogenesis) requires not only activation of endothelial cells, but also recruitment and proliferation of mesenchymal cells (pericytes, vascular smooth muscle cells), which form media and adventitia of the vessel wall. From gene targeting experiments it is known that vascular endothelial growth factor (VEGF) as well as platelet derived growth factor (PDGF) play a key role in establishing functionally active vessels, whereas not much data exist regarding the interaction between endothelial and mesenchymal cells, leading to maturation and assembly of the vessel wall. We therefore investigated the influence of angiogenic factors on the expression of PDGF in endothelial cells.

Results: Stimulation of endothelial cells (HUVECs) with VEGF (10-100 ng/ml) led to a marked, dose- and time-dependent induction of PDGF-isoform B, not isoform A at the level of mRNA, as shown by Northern blotting. Basic fibroblast growth factor (bFGF) did not alter expression of PDGF-B, whereas combination with VEGF resulted in a significant induction. These findings were confirmed at the protein level using Western blot. Since PDGF-BB is known to be a strong chemotactic agent for mesenchymal cells, we used conditioned medium from endothelial cells stimulated with VEGF in a microchemotaxis chamber, leading to a strong chemotactic response of mesenchymal cells (10T1/2 fibroblasts and vascular smooth muscle cells) towards the conditioned medium, comparable to the effect of 10 ng/ml PDGF-BB. The use of blocking PDGF-antibody attenuated the cell migration rate to 30%, further addition of HB-EGF-antibody completely abolished the chemotactic response.

Summary: VEGF, but not bFGF, induced expression of PDGF-B isoform in endothelial cells, which is a strong chemotactic agent for mesenchymal cells. VEGF might therefore indirectly participate in maturation and assembly of the vessel wall via this paracrine mechanism.

2614 Essential role of ICAM-1 mediated monocyte migration during arteriogenesis

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Previous studies have shown that blocking of ICAM-1 via monoclonal antibodies abolishes the MCP-1 induced effect on arteriogenesis (collateral artery growth). However, it is not yet clear whether ICAM-1 plays an essential role under physiologic conditions during arteriogenesis. In fact, it seems that it is a matter of numerous cell adhesion molecules (ICAM, VCAM, Selectins), responsible for monocyte transmigration and thus arteriogenesis. Methods: We therefore ligated the right femoral arteries of Selectin -/- mice, showing a defect of all three Selectin isoforms (E-, P-, L-Selectin), ICAM-1 -/- and their appropriate genetic backgrounds. Seven days later both hindlimbs were perfused under maximum vasodilation, combined with the injection of differently labeled fluorescent microspheres. Using FACS-analysis, the microspheres were quantified and perfusion ratios of both hindlimbs were calculated. Results: Results are expressed as perfusion of ligated vs. non-ligated hindlimb. ICAM -/- mice show a significant reduction of perfusion restoration after femoral artery ligation as compared to controls (ICAM-1 -/- 37.5 ± 11.9% vs. C57/BL6 63.8 ± 17.3%; $p<0.05$). The defect of the Selectin isoforms, in contrast, does not lead to a significant reduction of the arteriogenic response to the ligation of the femoral artery as compared to their backgrounds (Selectin -/- 32.4 ± 3.0% vs. Selectin WT 36.9 ± 9.8% p=0.33). Conclusion: A functional defect of only one cell adhesion molecule is usually only of small biological relevance, since others can take its role over. However, this study shows that not Selectin mediated rolling of leukocytes on the endothelium, but firm adhesion to ICAM-1 is essential during arteriogenesis.

2615 Inhibition of endothelial progenitor cell apoptosis via forkhead factor-dependent downregulation of the pro-apoptotic protein Bim

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Circulating bone marrow-derived endothelial progenitor cells (EPCs), which originate from CD34-positive hematopoietic stem cells, are involved in postnatal neovascularization. Transplantation of cultivated EPCs or CD34-positive cells enhances neovascularization and improves cardiac function. In hematopoietic cells, the forkhead transcription factors play an important role in apoptosis induction via the regulation of down-stream targets like the pro-apoptotic protein Bim. Therefore, we investigated the involvement of Bim in EPC apoptosis. EPC apoptosis was induced by H2O2 and determined by FACS analysis of annexin-positive cells. EPCs were isolated by density gradient centrifugation with Biocoll from peripheral blood of healthy subjects and cultured for 3 days before stimulation. H2O2 dose-dependently induces apoptosis of EPCs (500 μM: 288±94% of control). Consistent with apoptosis induction the number of differentiated EPCs was reduced after 48 h of H2O2 treatment (50±3% of control) as determined by counting dual-stained cells positive for lectin and DiLDL as a marker for EPCs. Because statins promote the phosphorylation and activation of the pro-survival kinase Akt, we analysed the effect of statins on the reduction of EPC number and apoptosis. Coincubation with atorvastatin (0.1 μM) significantly prevents the reduction of EPC number by H2O2 (178±2% of control; $p<0.05$). In addition, atorvastatin (0.1 μM) significantly reduces EPC apoptosis induced by H2O2 (288±94% vs. 146±31% of control; $p<0.05$). The anti-apoptotic effect of atorvastatin could be reversed with the PI3K-inhibitor Ly294002 (273±8% of control). Because the pro-apoptotic forkhead transcription factors (AFX, FKHR, FKHRL1) are phosphorylated and thereby inactivated by the PI3K/Akt pathway, we analysed the effect of atorvastatin on the phosphorylation of AFX. Atorvastatin (0.1 μM) induces the phosphorylation of AFX. In addition, atorvastatin profoundly reduces the expression of the forkhead-regulated pro-apoptotic Bcl-2-family member protein Bim in EPCs after 24 h (37±8% of control) in a PI3K-dependent manner and inhibits the H2O2-induced upregulation of Bim (165±14% vs. 112±19% of control), suggesting a potential involvement of Bim in EPC apoptosis. Taken together, these results provide insights into the beneficial effects of statins. Atorvastatin reduces apoptosis of EPCs induced by oxidative stress, inactivates the forkhead factor AFX and downregulates the expression of the pro-apoptotic protein Bim.

2616 Cooperative control of Akt phosphorylation and apoptosis by cellular cytoskeletons (CSKs) in capillary endothelial cells

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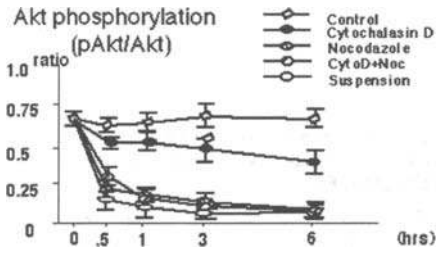
Capillary endothelial cells can be switched between growth and apoptosis by modulating their shape using micropatterned adhesive islands (Chen et al., Science 1997; 276:1425-1428). To examine whether cytoskeletal filaments like actin and tubulin contribute to this apoptotic respons, we carried out chronospatial analysis of PI3 kinase-Akt signaling pathway and apoptosis rate as well as cellular morphometry with CSK disrupting drugs. The cell shape and intracellular changes were visualized in living cells with YFP-actin or GFP-tubulin. Disruption of microfilaments or microtubules using cytochalasin D (Cyto D; 1μg/mL) or nocodazole (NOC 10μg/mL) led to levels of apoptosis in capillary cells equivalent to that demonstrated by inducing cell rounding using micropatterned culture surfaces containing small (< 20 μm diameter) circular adhesive islands (CytoD:NOC:island=12%:20%:18%). Simultaneous disruption of microfilaments and microtubules led to more pronounced cell rounding and to enhanced levels of apoptosis approaching that observed during anoikis in fully detached cells (CytoD+NOC:suspended=48%:55%), indicating that these two cytoskeletal filament systems can cooperate to promote cell survival. Western blot analysis revealed that the protein kinase, Akt, which is known to be critical for control of cell survival became dephosphorylated during cell rounding induced by disruption of the cytoskeleton, and that this was accompanied by a decrease in bcl-2 expression and an increase in caspase activation.



Akt phosphorylation after attachment.

This ability of the cytoskeleton to control capillary endothelial cell survival should be important for understanding the relationship between extracellular matrix turnover, cell shape changes, and apoptosis during angiogenesis inhibition.

2617 Endothelial progenitor cells modulate vascular re-endothelialization and neointima formation. Effect of HMG CoA reductase inhibition

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Background: Both, atherosclerosis and restenosis after vascular injury are characterized by endothelial dysfunction and apoptosis, inappropriate endothelialization and neointima formation. Bone-marrow-derived endothelial progenitor cells have been implicated in neovascularization resulting potentially in adult blood vessel formation e.g. in the heart subjected to myocardial infarction. Despite the anticipated stem cell plasticity, the role of bone-marrow-derived endothelial progenitor cells has not been clarified in vascular lesion development.
Methods and Results: We investigated vascular lesion formation in mice which had undergone transplantation of bone-marrow transfected by means of retrovirus with enhanced green fluorescent protein. Carotid artery vascular injury was induced resulting in profound neointima formation. Fluorescent microscopy and immunohistological analysis revealed that circulating endothelial progenitor cells derived from the bone marrow are decisively involved in re-endothelialization of the vascular lesions. Treatment with an HMG CoA reductase inhibitor, rosuvastatin 20 mg/kg/d enhanced the circulating pool of endothelial progenitor cells by 5-fold, propagated the advent of bone-marrow-derived endothelial cells in the injured vessel wall and, thereby, accelerated re-endothelialization and significantly decreased neointima formation.
Conclusions: Vascular lesion development initiated by endothelial cell damage is moderated by bone-marrow-derived endothelial progenitor cells. HMG CoA reductase inhibition promotes bone marrow-dependent re-endothelialization and diminishes vascular lesion development. These findings may help to establish novel pathophysiological concepts and may enable future therapeutic strategies of various cardiovascular diseases.

2618 Increase of circulating endothelial progenitor cells in patients with coronary artery disease after reversible exercise-induced ischaemia

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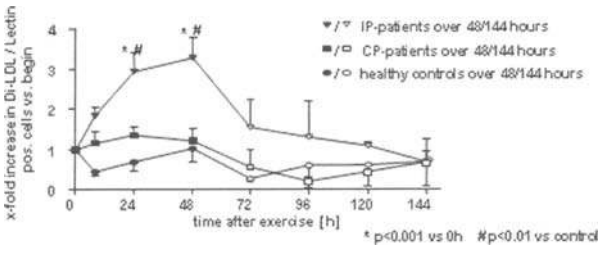
Increasing evidence suggests, that endothelial progenitor cells (EPC) play an important role in postnatal neovascularization. As animal studies propose ischemia seems to be one of the main triggers for the release of EPC's from the bone marrow. Aim of this study was therefore to analyse the effect of a maximal stress test on the number of EPC's in patients with coronary artery disease (CAD) and exercise-induced myocardial ischemia (ischemic patients, IP, n=16) versus CAD-patients without exercise-induced ischemia (control patients, CP, n=6) and healthy subjects (HS, n=6).
The concentration of EPC's was analyzed by FACS-analysis and cell culture assay in blood samples drawn before and up to 144h after the ergometer test. The amount of EPC's among the adherent cells was determined by analyzing Di-LDL and FITC-labeled lectin double positive stained cells by Laser Scanning Cytometry (Fig.1). Plasma concentrations of VEGF, b-FGF, TNF-alpha and GM-CSF were determined by ELISA.
Circulating EPCs increased in IP with a maximum after 24-48h (cell culture: 3.3±0.6fold increase, p=0.001 vs. baseline, p=0.01 vs. CP/HS; FACS: 3.1±0.5fold increase, p=0.001 vs. baseline, p=0.01 vs. CP/HS) and returned to baseline levels within 72h. In CP and HS no increase in EPCs was detectable. VEGF levels in IP reached a maximum after 2h (4.0±1.1fold increase, p=0.001 vs. baseline, p=0.03 vs. CP/HS) whereas no change was observed in CP and HS. The deltas of VEGF and EPC were significantly correlated (r=0.77; p<0.001).



In conclusion, the present study demonstrates for the first time that a short episode of myocardial ischemia in CAD patients is sufficient to induce a considerable increase in the number of circulating EPC's. This rise seems to be related to the previous increase of plasma VEGF.

SIGNAL TRANSDUCTION PATHWAYS IN CARDIAC HYPERTROPHY AND FAILURE

2619 Cardiac hypertrophy due to pressure overload correlates with increased active cardiac elongation factor-2 in senescent rats

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Eucaryotic elongation factor-2 (eEF-2), a cytosolic GTPase of 857 amino acids, is a key protein of peptide-chain elongation during protein synthesis. Endogenous ADP-ribosylation at a unique posttranslationally modified histidine residue, called diphthamide,leads to its inactivation. A close relationship between protein synthesis (PS) and the amount of eEF-2 has been demonstrated for several tissues and cell systems. Furthermore an involvement of eEF-2 in the slowing down of bulk PS during ageing has been proposed. Therefore we studied the influence of experimental cardiac hypertrophy on total and active (i.e. not endogenously ADP-ribosylated) eEF-2 in cardiomyocytes (CM) from adult rats in correlation with cardiac PS and ageing.

Methods: Left ventricular (LV) hypertrophy was induced in 4 week old Wistar rats by stenosis of the suprarenal abdominal aorta (AOB). Sham-operated animals underwent the identical procedure except the hemoclip (SOP). CM were isolated according to the LANGENDORFF method at 8, 20 and 52 weeks after OP. PS of the CM was assessed using [3H]-phenylalanine incorporation. Active eEF-2 was measured after specific labelling of cytosolic extracts of the CM with Pseudomonas exotoxin A catalyzed [32P]ADP-ribosylation and SDS-PAGE,total amount of eEF-2 was detected by immunoblot.

Results: LV hypertrophy was confirmed by a significantly increased heart weight of the old AOB rats (1.88±0.1g;n=7)compared to 8 weeks postoperative AOB (1.43±0.13g;n=3)and old SOP rats (1.38±0.08g;n=6). Basal PS continually decreased in both groups (AOB and SOP 8 weeks postop. 1726±28 and 1648±36 dpm; AOB and SOP senescent 814±46 and 602±53 dpm respectively). PS was significantly higher in AOB compared to SOP only in the senescent animals ($p<0.05$). Active eEF-2 was elevated by 153% in the old-aged AOBs compared to SOPs ($p<0.05$). An age dependent decline in active eEF-2 in SOPs could not be demonstrated. These results were confirmed by immunoblot.

Conclusions: The positive correlation of active eEF-2 with the increased heart weight and the PS of senscent AOB rats compared to old-aged SOP rats points at an involvement of eEF-2 in the hypertrophic reaction of the heart due to pressure overload. Old and young adult rat hearts showed a different reaction pattern of eEF-2 in this stress situation.

2620 Activation of distinct signal transduction pathways in hypertrophied hearts by pressure and volume-overloads

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Background: Chronic pressure- and volume-overloads result in morphologically and functionally distinct types of cardiac hypertrophy. A key role of mitogen-activated protein (MAP) kinase family in cardiomyocyte hypertrophy has been demonstrated in in vitro studies using neonatal cardiomyocytes and in vivo pressure-overload hypertrophy. However, signal transduction pathways leading to eccentric cardiac hypertrophy induced by volume-overload have not been rigorously investigated. Thus we examined the phosphorylation activities of 3 subfamilies of MAP kinases including extracellular signal-regulated kinase (ERK1/2), p38 MAP kinase, and c-Jun NH2 terminal kinase (JNK) and Akt in rabbit hearts with volume-overload. Methods: Volume-overload was induced by shunt formation between the left common carotid artery and the external jugular vein. Subtotal ascending thoracic aortic banding was performed in rabbits and these were used as a model for pressure-overload hypertrophy. Phosphorylation activities of ERK1/2, p38 MAP kinase, JNK, and Akt were examined by Western blotting with phospho-specific antibodies. Results: Chronic volume-overload increased left ventricular weight (4.1 ± 0.2 vs. 6.2 ± 0.3 g, $P < 0.01$) with ventricular cavity dilatation (12.8 ± 0.5 vs. 17.5 ± 0.5 mm, $P < 0.01$), and relative wall thickness was decreased indicating eccentric cardiac hypertrophy. Chronic pressure-overload increased left ventricular weight ($P < 0.01$) with no cavity dilatation, and relative wall thickness was increased. In rabbit hearts with concentric hypertrophy by ascending thoracic aortic stenosis, ERK1/2 ($P < 0.05$), p38 MAP kinase ($P < 0.01$) and Akt ($P < 0.05$), but not JNK, were activated 1 day and 1 week after banding surgery and the activity was returned to normal levels after 4 weeks. However in rabbit hearts with eccentric hypertrophy by volume-overload, none of ERK1/2, p38 MAP kinase and JNK were activated from 1 day to 12 weeks after shunt formation. Akt was predominant in volume-overloaded hearts, and the activation of Akt was sustained from 1 day to 12 weeks after shunt surgery ($P < 0.01$). Conclusion: These results suggest that different mechanical stresses activate distinct signaling pathways, which may lead to different types of cardiac hypertrophy.

2621 Inhibition of extracellular signal-regulated kinase prevents progressive left ventricular remodelling in hypertensive heart failure

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Background: Mitogen-activated protein kinases (MAPKs) are activated in response to neurohormonal activation in left ventricular (LV) hypertrophy and heart failure. We studied whether inhibition of MAPKs is effective in preventing LV dysfunction and remodeling in a model with angiotensin II-driven LV dysfunction.

Methods: We monitored LV function, neurohormones, and activation of MAPKs in homozygous REN2 rats at different time-points (6, 10, and 13 weeks). Then, we treated REN2 rats before the onset of heart failure (7-11 weeks), with placebo, an AT1 receptor blocker (ARB, candesartan), an extracellular signal-regulated kinase (ERK) inhibitor (Tyrphostin A46), or a p38 MAPK inhibitor (SB 239063). We studied LV function, neurohormonal profile, MAPK activity, and LV histological morphometry (fibrosis and microvessel density).

Results: LV hypertrophy (LVH) was present in REN2 rats at all time-points, and LV dysfunction progressed to heart failure between 10 and 13 weeks. Blood pressure was elevated after 6 and 10 weeks, but normalized after 13 weeks. Plasma neurohormones (renin, N-ANP) were elevated. ERK was activated at early time points (6, 10 weeks); this abated during heart failure. P38 MAPK was not activated. Treatment with the ARB prevented LVH and RVH, normalized LV end-diastolic pressure (LVEDP) and dP/dt, N-ANP levels, hampered fibrosis, and restored microvessel density (all: $P<0.05$). ERK inhibition reduced LVH and LVEDP ($P<0.05$), and markedly reduced fibrosis and restored microvessel density (both $P<0.01$). Myocardial ERK activation was blocked by ERK inhibition. The P38 MAPK inhibition reduced LVH ($P<0.05$), however no effects on other outcome parameters were observed.

Conclusions: ERK is activated in this model of LVH and heart failure. Treatment with an ERK inhibitor is efficacious in preventing LV remodeling, and its effects resemble the effects of the ARB. Especially, fibrosis was reduced and microvessel density was restored, which indicate that the observed ERK activation may not be confined to the cardiomyocytes, but may also be present in fibroblasts and endothelial cells.

2622 Decreased activation of the JAK2–STAT3 signaling pathway in patients with end-stage dilated cardiomyopathy

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Interleukin-6 (IL-6) related cytokines signaling via the common receptor subunit gp130 and activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway provide a critical myocyte survival pathway. Little is known, regarding the activation of this signaling pathway in the myocardium of patients with end-stage dilated cardiomyopathy (DCM).

We have performed a comprehensive expression analysis in left ventricular myocardium derived from patients with end-stage DCM (n=10) and non-failing (NF) donor hearts (n=5) concerning IL-6 related cytokines (IL-6; leukemia inhibitory factor, LIF; cardiotrophin-1, CT-1), receptors (gp130; LIF-receptor, LIFR; IL-6-receptor, IL-6R), signal transducers (JAK2; STAT1; STAT3) and signal transduction inhibitors (suppressors of cytokine signaling, SOCS-1 and SOCS-3) (table).

IL-6	LIF	CT-1	IL-6 receptor	LIF receptor	GP130	JAK2	STAT1	STAT3	SOCS1	SOCS3
-60%**	+48%*	-21%	-7%	-17%*	+20%	-9%	-15%	-58%**	+70%*	-40%**

Altered protein-expression in failing versus non failing heart (STAT: Signal transducer and activator of transcription, SOCS: suppressor of cytokine signaling, CT-1: cardiotrophin 1. *$p<0,05$, **$p<0,01$)

In addition, tyrosine phosphorylation (i.e. activation) of JAK2 (-72%, $p<0.01$) and STAT3 (-53%, $p<0.01$) were significantly reduced in end-stage DCM, whereas STAT1 tyrosine phosphorylation was unchanged.

Conclusion: Signaling through gp130 and JAK-STAT is profoundly altered in patients with end-stage DCM. Most notably, protein expression and tyrosine phosphorylation of STAT3 and protein expression of SOCS3 are significantly reduced, suggesting altered STAT3 dependent transcription in end-stage dilated cardiomyopathy.

2623 Differential regulation of mitogen-activated protein kinases in the failing human heart in response to mechanical unloading

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Background: Mechanical unloading of the heart with a left ventricular assist device (LVAD) leads to favorable changes in the biology of the failing cardiac myocyte. To determine a potential mechanism for these improvements, we examined the regulation of mitogen-activated protein kinases (MAPKs) in the failing heart in the presence and absence of LVAD support.
Methods and Results: We examined the degree of activation (ie, phosphorylation) of p44/42 extracellularly regulated kinase, p38 kinase, and c-Jun N-terminal kinase (JNK1/2), and the corresponding activity levels of these MAPKs in myocardial samples obtained from 11 patients with LVAD support and in 11 patients without LVAD support. MAPK activity was also examined in an additional 6 patients from whom paired samples were obtained before and after LVAD support. The activity of p44/42 and JNK1/2 were reduced significantly, whereas p38 activity levels were significantly increased after LVAD support. We examined functional parameters that are linked to MAPK activation, namely cardiac myocyte hypertrophy and apoptosis. Both cardiac myocyte cell size and the incidence of cardiac myocyte apoptosis were significantly reduced after LVAD support.
Conclusions: Mechanical unloading of the failing heart leads to differential regulation of MAPKs. These changes in MAPK activity are associated with changes in myocyte hypertrophy and viability, suggesting a potential mechanistic basis for some of the observed salutary changes after LVAD support.

REVASCULARIZATION THERAPY IN THE ELDERLY

2625 Acute coronary syndromes in the elderly: insights from the GRACE registry

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Elderly patients are believed to be at high risk of acute coronary syndromes (ACS) but an optimal strategy for treatment is still under debate.
Methods: The Global Registry of Acute Coronary Events (GRACE) collects data from 10,000 cases of ACS worldwide each year. We analysed treatment and outcomes of the first 8,564 ACS patients aged 65 and over.
Results: Patients >= 75 years were treated significantly less aggressively than younger patients, but had a significantly higher rate of death and major bleeding (table). In multivariate models adjusting for potential confounders the odds ratios(OR 95% confidence interval) for patients >= 75 years vs. those 65 to 75 for death and major bleeding remained unchanged and significant, the ORs were 1.90 (1.58, 2.29) and 1.55 (1.24, 1.93), respectively. Elderly patients with renal insufficiency appear to be at a high risk, with creatinine >1.29 being a strong predictor for death OR 3.22 (2.69, 3.86) and major bleeding OR 1.97 (1.58, 2.46). Mortality was lower, when aspirin OR 0.45 (0.35, 0.57), or low molecular weight heparin (LMWH) OR 0.67 (0.56, 0.80) are used. Major bleeds occur more frequently with the use of GPIIb/IIIa inhibitors OR 2.08 (1.58, 2.74), PCI OR 1.90 (1.47, 2.47) and unfractionated heparin OR 1.55 (1.21, 1.98), while under LMWH therapy major bleeds occurred significantly less OR 0.68 (0.54, 0.86).

		Age group		P-value
		≥75 years	65-75 years	
Treatment	GpIIb/IIIa	13.5%	16.9%	<0.0001
	Thrombolytics	11.9%	16.1%	<0.0001
	Cardiac Cath	37.5%	51.7%	<0.0001
	PCI	21.1%	28.1%	<0.0001
	CABG	4.4%	7.8%	<0.0001
Outcomes	Hospital Death	10.6%	5.3%	<0.0001
	Major Bleed	5.5%	3.7%	<0.0001

PCI - percutaneous coronary intervention; CABG - coronary artery bypass grafting.

Conclusion: These data show that the benefits of modern antithrombotic/antiplatelet therapies and interventional cardiac procedures extend to the population >75 years of age, and that such therapies should probably be used on a wider scale than at present.

2626 Treatment and outcome in an unselected elderly population with acute myocardial infarction: 6-month follow-up results

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Background: Reperfusion treatment (RT) is considered particularly beneficial in higher risk subgroups, including the elderly. Primary PTCA (P-PTCA) is the most frequent modality of RT in the Florence area (Italy). Scanty data exist about the use of P-PTCA and the outcome in an unselected elderly population.
Methods: Data are derived from the AMI-Florence Registry, a prospective observational registry including all the Florence area residents who experienced AMI from March 1, 2000 to February 28, 2001 and were admitted to hospital within 24 hours from symptom onset. The analysis concerning the 806 patients (pts) with ST-elevation AMI included in the registry is presented.
Results: Of these pts, 368 (46%, mean age: 58 yrs) were <70 yrs (Group 1) and 438 (54%, mean age: 79 yrs) were >=70 yrs (Group 2). No difference was observed in time from symptom onset to hospital admission between groups. RT was used in 73% of Group 1 pts (P-PTCA in 93%) and in 51% of Group 2 pts (P-PTCA in 90%) (p=.001). Of the Group 2 pts directly admitted to the 2 centres with P-PTCA facilities, 73% underwent RT (99% with P-PTCA) while only 39% of the Group 2 pts admitted to the 5 hospitals without invasive facilities were treated with RT (78% with P-PTCA, performed after patient transfer) (p=.001). At multivariate analysis age >=70 yrs was negatively associated with the use of RT (OR: 0.52, 95%CI: 0.35-0.74). In pts not treated with RT, in-hospital mortality was 7% in Group 1 and 20% in Group 2 (p=.004); 6-month mortality was 10% and 30%, respectively (p=.001). In pts treated with RT, in-hospital mortality was 1% in Group 1 and 11% in Group 2 (p=.001), 6-month mortality was 3% and 17%, respectively (p=.001). At multivariate analysis age >=70 yrs was associated with a reduced probability of survival (OR: 0.33, 95%CI: 0.19-0.57). The use of RT showed a protective effect in Group 2 pts (OR: 1.62, 95%CI: 0.99-2.64), while it did not show a significant effect in Group 1 pts (OR: 1.45, 95%CI: 0.42-5.07).
Conclusion: Even in a setting where P-PTCA is the preferred modality of RT, elderly pts are less likely to undergo RT, particularly if they are admitted to a community hospital without invasive facilities. The results suggest a protective effect of RT in pts >=70 yrs.

2627 Surgical revascularization and percutaneous coronary intervention, in the setting of myocardial infarction, are more efficacious in the elderly

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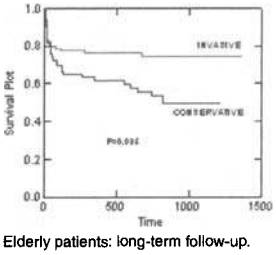
Little is known, especially in the elderly, about the role of surgical myocardial revascularization and percutaneous coronary intervention (invasive procedures - IP) in the long-term follow-up of pts with acute myocardial infarction (AMI), aim of this study.
Methods: we analyzed 481 pts with AMI included prospectively and consecutively in a databank and followed for up to 4 years (mean survival time 3.15 y). During the in-hospital phase, 309 pts were submitted to IP (64.2%), and 151 (31.4%) were older than 69 years. Pearson Chi-square was utilized for the in-hospital analysis; Kaplan-Meier estimator and log-rank test were utilized in the long-term follow-up analysis.
Results: (a) In-hospital analysis: for the elderly population, the mortality rate was 21.8%; the mortality rates for the subgroups submitted to IP (n=85) or treated conservatively were, respectively, 18.8% and 24.2% (OR=0.78, p=0.53); for pts younger than 70 y, the mortality rate was 5.5%; the mortality rates for the invasive (n=224) or conservative subgroups were 6.2% and 4.7%, respectively (OR=1.35, p=0.58). (b) Long-term follow-up analysis: the survival rates for invasive and conservative groups in the whole population were, respectively, 83.1% ± 2.3 and 70.6% ± 3.8 (p=0.007); in the subgroup of pts older than 69 y the survival rates were 74.8% ± 4.8 and 49.7% ± 7, respectively (p=0.035); in the subgroup of pts younger than 70 y, the survival rates were 86.3% ± 2.5 and 83.1% ± 3.9 (p=0.7). Sixty-three pts were treated with primary angioplasty (24 and 39, respectively, for the elderly and younger groups). The exclusion of these pts did not modified the main results.



Elderly patients: long-term follow-up.

Conclusion: In conclusion, in the long-term follow-up post-AMI, the invasive strategy was more efficacious in elderly patients.

2628 Is the early hazard of revascularisation for chronic coronary artery disease in elderly patients balanced during long-term follow-up?

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Background: The Swiss multicenter Trial of Invasive versus Medical therapy in Elderly patients (TIME) showed, that patients 75 years of age or older with chronic angina benefit significantly more from invasive (INV) than from optimal medical (MED) therapy regarding quality of life (QoL) and outcome after 6 months, although at a non-significant excess in early mortality.
Aim/Methods: To assess the long-term risk/benefit ratio of INV therapy in these patients, all 282 patients, age 80±4 years, surviving the first 6 months (140 randomized to INV and 142 to MED therapy) were followed prospectively after 12 months for QoL (angina severity by Canadian Cardiac Society class, Rose score; general health by SF-36; daily activity by Duke Activity Score Index) and major adverse clinical events (MACE: death, infarction, hospitalisation for acute coronary syndrome ± (repeat) revascularisation).
Results: Angina and QoL improved significantly after 6 and 12 months for both INV and MED therapy vs. baseline ($p<0.01$ each), but the difference in QoL between treatments in favour of INV patients noted after 6 months disappeared after 12 months due to 46% MED patients crossing over to revascularisation. The benefit in angina and QoL of MED patients without revascularisation remained significantly lower than that of INV patients after 6 and 12 months ($p<0.05$). Mortality for each 6 months period (0-6 and 7-12 months) decreased in INV patients by 66% from 8.5% to 2.9%, whereas it stayed unchanged in MED patients (4.1% and 4.2%). MACE rates were significantly higher for MED patients after 6 months (49% vs. 19% INV, $p<0.001$), a difference which increased to 72% (MED) vs. 28% (INV) after 12 months ($p<0.0001$).
Conclusions: Both treatment strategies led to a persistent improvement in angina and QoL, but the difference in favour of INV therapy after 6 months disappeared after 12 months due to an increasing rate of revascularisations in MED patients. The small early mortality hazard of INV therapy was reversed during months 7-12 and the overall advantage of INV therapy in reduction of MACE even increased. Thus, the benefits of INV compared to MED therapy outweigh the early risks during late follow-up.

2629 Ischaemic heart disease in the elderly and referal patterns for revascularisation

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Demographic analysis continues to show a disproportionate increase in the size of the elderly population. IHD is responsible for 25% of medical admissions within this age group. While being more likely to be intolerant of medical therapy, these patients are believed to be less likely to receive revascularisation.
Objectives: To establish the incidence of IHD in the elderly presenting acutely to hospitals in the Merseyside & Cheshire zone and to investigate referral patterns for revascularisation in the elderly.
Method: Data on the number of acute adult medical admissions from 1/4/99 to 30/3/00 broken down by age and diagnosis was obtained from 11 hospitals in the Merseyside & Cheshire zone. Data on angiography and revascularisation was obtained by searching the procedures databases at the Cardiothoracic Centre Liverpool, which is the sole tertiary referral center for the zone.
Results: Over one year there where 125,755 acute medical admissions of which 56,692 (45%) where over the age of 70yrs and 22.5% where due to IHD. See table for a breakdown by age of the number of admissions due to IHD, coronary angiograms, PTCA & CABG performed.

Coronary angiograms & revascularisation

Age	Admissions with IHD	Corronary Angiograms	PTCA	CABG
All Adult	28,314	3354	924	1034
>70yrs	14,200(50%)	638 (19.0%)	114(12.3%)	226(21.9%)

Conclusion: An elderly patient with IHD is markedly less likely to be referred for angiography, however once an angiogram has been performed the likelihood of going on to receive CABG is similar to that in younger patients. The number of PTCAs is relatively reduced which we believe is due to the high incidence of multi vessel disease. Given that the chance of revascularisation is only marginally less (9.1%) we believe there is a case for lowering the threshold for angiogrophy in this group of patients.

2630 Is coronary revascularisation underused among older people? – Prospective findings from the ACRE study

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Objective: To determine whether coronary revascularisation is underused in older patients, using appropriateness ratings as a marker of clinical need.
Design: Prospective cohort study with 2.5 years follow up. A nine member expert panel rated the appropriateness of revascularisation independently of patient age.
Setting: Tertiary cardiac centre in the City and east London.
Patients: 4020 consecutive patients undergoing coronary angiography in the Appropriateness of Coronary Revascularisation (ACRE) study. There were no exclusion criteria. There were 2601 patients aged <65 years, 1162 aged 65-74 years and 250 aged 75-84 years; median age 62 years.
Main outcome measures: Coronary revascularisation, all cause mortality.
Results: Among the 1353 patients in whom CABG was deemed appropriate, older compared to younger patients were equally likely to undergo CABG (patients aged 75-84 years vs <65 years hazard ratio 1.29, 95% confidence interval(CI) 0.97-1.71). All cause mortality was higher among patients for whom CABG was deemed appropriate but who underwent medical management compared to those who received CABG: the hazard ratios were 2.83 (95%CI 1.60-5.01) in patients aged <65 years, 4.62 (95%CI 2.54-8.40) in patients aged 65-74 years and 7.29 (95%CI 2.19-24.23) in patients aged 75-84 years after adjustment for number of diseased vessels, left ventricular function and Parsonnet operative risk score. The absolute risk differences in these three age groups were 8.3%,18.3% and 35.3% respectively. Coronary angioplasty among patients in whom it was deemed appropriate was performed at a lower rate in patients aged 65-74 years compared to patients aged <65 years, hazard ratio 0.69 (95%CI 0.54-0.90).

Age group	Medical		CABG		Medical:CABG
	Number of deaths	Absolute risk (%)	Number of deaths	Absolute risk (%)	
<65	27	13.17	21		
65-74	31	24.41	17		
75-84	9	42.86	4		

Conclusions: The mortality impact of underuse of CABG may be greater among older patients in relative and absolute terms. With the lack of randomised trials of revascularisation among older age groups, appropriateness ratings offer a useful method of investigating age inequalities in treatment.

GENDERS DIFFERENCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE

2631 Gender differences in the treatment of coronary heart disease?

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It has been suggested that women are under diagnosed and under treated for coronary heart disease in relation to men. We therefore analysed a consecutive group af daily routine patients, referrred to the cath. lab. with suspicion of, or established diagnosis of coronary heart disease. All patients came from a well defined geographical area and follow up with respect to death is 100% complete, with the longest follow up period of 6 years.

The material represents 2.651 patients, 794 women mean age 63 year (SD 11,7) and 1.857 men mean age 61 year (SD 10,9). The proportion of acute examinations were 33,1% among the females and 32,4% among the males.

Coronary pathology: The patients were divided in to 3 groups. Group 1 consisted of patients with normal coronary arteries. Group 2 of patients with light to moderate (diffuse insignificant or 1-2 vessel) disease. Group 3 of patients with severe (3 vessel and/or left main) disease. 20.5% of the women vs. 4.5% of the men ($p<0.001$) had normal coronary arteriograms. 60.3% of the women vs. 62.4% of the men had light to moderate disease (ns). 19.1% of the women vs. 33.1% of the men had severe disease ($p<0.001$)

Treatment: Revascularisation of patients in group 2 and 3 was performed as either PCI or CABG. 67.2% of the women vs. 75.8% of the men in group 2 was revascularised ($p<0.001$). This significant difference is due to the fact that the men had more 2 vessel disease than the women in this group (data not shown). In group 3 with severe disease 89.5% of the women vs. 86.4% of the men was revascularised (ns).

Survival: Within the 3 different groups of coronary pathology there was no difference in survival between women and men. After revascularisation the relative risk of death (men vs. women) was 0.98 (95 CI 0.68-1.42) after correction for age, coronary pathology, acute procedure and year of treatment.

Conclusion: In our material of unselected routine patients, we find no evidence of under treatment of women with coronary heart disease, but women have a lesser degree of disease when examined. For equal degree of disease, women and men were treated alike, and with the same outcome with respect to survival.

2632 In-hospital management of acute myocardial infarction in France: is there a gender bias?

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The possibility of a "sex bias" in the management of patients with coronary artery disease is controversial. We conducted a nation-wide in 369 intensive care units representing more than 3/4 of all French ICUs in November 2000, in order to asses "real world" management and outcome of patients with acute myocardial infarction (AMI). A total of 2320 patients with AMI < 48 hours from symptom onset were included. There were 1692 men (73%) and 628 women (27%). Women were older than men (73 ± 13 vs 63 ± 14 years, $p<0.0001$). Risk factors differed markedly, hypertension 40% vs 63%, current smoking 33% vs 4%, known hyperlipidemia 40% vs 13%, diabetes mellitus 18% vs 28% in men and women, respectively. Women had less previous history of myocardial infarction (13% vs 20%), previous PTCA (5% vs 11%), previous CABG (2.6% vs 4.9%), peripheral artery disease (6% vs 10%), but more history of congestive heart failure (8.8% vs 5.6%). Reperfusion therapy by either intravenous thrombolysis or PTCA was used more seldom in women (36% vs 46%, $p< 0.0001$). Heparin, nitrates, calcium antagonists, and ACE-inhibitors were used as often in men and women. In contrast, GP IIb/IIIa blockers (20% vs 12%), beta-blockers (74% vs 63%) and statins (49% vs 34%) were used more often in men, while diuretics (23% vs 36%) were used more often in women.

Using multivariate regression analysis, however, most classes of medications were not influenced by gender. In particular, gender was not an independent predictor of reperfusion therapy, antiplatelet agents, and beta-blockers. The same was true for diuretics, digitalis, and intravenous dobutamine. Only statins (relative risk: 0.72; 95% CI/0.59-0.88) and GP IIb/IIIa blockers (relative risk: 0.74; 95% CI: 0.56-0.98) remained negatively correlated with female sex. During the hospital stay, 62% of men and 45% of women underwent a PTCA procedure ($p< 0.0001$); this difference remained statistically significant after multivariate adjustment (RR: 0.77; 95% CI: 0.63-0.95).

Conclusion: women admitted for AMI are 10 years older on average than men. As evidenced by multivariate analyses, this age difference explains most of the differences in their management compared to men. A "sex bias", however, cannot be formally excluded as regards the use of PTCA during the initial hospital stay.

2633 Use of revascularisation procedures in women after acute coronary events: results from the French nation-wide PREVENIR Survey

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There are controversial data about gender differences in the management of coronary artery disease. In a large sample, we compared the use of revascularisation procedures after acute coronary events, in French men and women, at the end of the nineties.

Methods: An observational survey was carried out in 149 intensive cardiac care units, evenly distributed in France. Seventy seven centres included 1334 patients in January 1998 and 72 other centres included 1292 patients in May-June 1999. Eligible patients were consecutive patients admitted for myocardial infarction (MI) or unstable angina in one of the participating centre and who were alive at discharge. Data were retrospectively collected from medical records after discharge (age, previous medical history, cardiovascular risk factors, left ventricular ejection fraction (LVEF) and therapeutic management of the acute coronary event).

Results: The sample was composed of 1921 men (73.2%) and 705 women (26.8%). Women were significantly older than men and less frequently admitted in a university hospital. Arterial hypertension and reduced LVEF were significantly more prevalent in women, whereas smoking was significantly more prevalent in men. Among patients admitted for MI, 79 women (19.3%) and 382 men (32.5%) were treated with pre-hospital or in-hospital thrombolysis, $p<0.0001$ for Chi 2 test. During the hospitalisation, percutaneous transluminal coronary angioplasty (PTCA) was performed in 164 women (40.1%) and 587 men (50.0%) admitted for MI ($p<0.001$) and in 104 women (35.1%) and 354 men (47.5%) admitted for unstable angina ($p<0.001$). In multiple logistic regression, adjustment variables were assessed by backward analysis among age, previous history of coronary artery disease, cardiovascular risk factors, LVEF and year and centre of inclusion (university hospital, general hospital or private clinic). The adjusted female-to-male odds ratio (OR) for the use of thrombolysis was 0,65 (95% confidence interval [0.49-0.87]). The adjusted OR for the use of PTCA was 0.72 [0.54-0.96] in patients admitted for unstable angina and 0.97 [0.75-1.25] in patients admitted for MI.

Conclusion: Women were less likely than men to receive thrombolysis for myocardial infarction and to be treated with PTCA when admitted for unstable angina. Although these results could reflect gender differences in the prevalence of contra-indications, an authentic discrimination against women in the management of coronary artery disease cannot be excluded.

2634 Health status outcomes of CABG patients one year post-surgery: are there gender differences?

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Introduction: This study evaluated health outcomes of coronary artery bypass patients (CABG) patients. Gender-specific outcomes were compared since research indicated differences in other cardiac groups.
Method: CABG patients (n=280;76% male) in three centres were interviewed prior to surgery. Follow-up questionnaires were posted to study participants at six weeks, six months and one year post-surgery. The questionnaire assessed symptoms (Seattle Angina Questionnaire) physical functioning (Duke Activity Scale Index), general health status (SF-36) and mental health (Hospital Anxiety and Depression Scale).
Results: Significant improvements were found from pre-surgery to one year post-surgery scores across all dimensions assessed; most improvement took place by 6 months. Adjusting for age, men had significantly higher levels of physical functioning and energy and lower levels of pain than woman prior to surgery ($p<0.01$). Six weeks post-surgery there was one significant difference; men reported higher levels of physical functioning ($p<0.01$). At six months post-surgery, in addition to better physical function, men reported better mental health and less pain ($p<0.01$). At one year post-surgery men reported significantly higher levels of physical functioning and general health status and lower frequency of angina and depression ($p<0.01$).
Conclusions: While male CABG patients reported better physical functioning than their female counterparts at all stages, there were few other differences between the groups either prior to surgery or at six weeks post-surgery. By six months post surgery, the experiences of both groups began to diverge with men performing better. At one year post-surgery this divergence continued with male CABG patients outperforming females in both rate and extent of recovery. This was represented by significantly better scores across a range of functional, health status, symptom and mental health measures. The clinical significance of age adjusted gender differences needs further evaluation.

2635 Signs of failed reperfusion or recurrent ischaemia – Worse for women?

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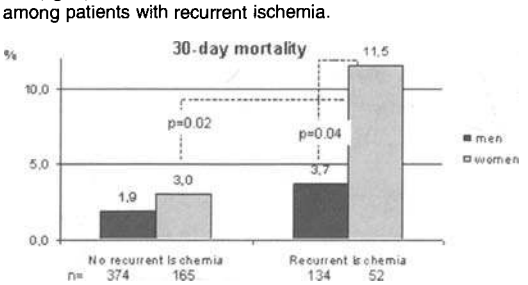
Introduction: Gender-differences in symptoms, signs and treatment of acute myocardial infarction have previously been suggested. We set out to investigate whether risk-stratification by ST-analyses may be done equally good in men and women. ST-segment resolution (ST-res) is a good predictor of both reperfusion and prognosis in patients with ST-elevation infarction (STEMI). Furthermore, ST-reelevations have been associated with worse outcome.
Methods: 864 patients with STEMI but without bundle branch block were included in the ST-monitoring substudy of the ASSENT 2 and ASSENT PLUS trials. Bad quality-, short-, and lost recordings were excluded, leaving 752 patients (527 men and 225 women) to analyse. Patients received either t-PA or TNK and were ST-monitored for 24 hours (h) with either vectorcardiography (n=571) or 12-lead ST-monitoring (n=181). ST-data were analysed blindly by two independent observers. We used 50% ST-res within 60 min as cut-off for early ST-res. Late, recurrent ischemic episodes were defined as any re-elevations after 4h, >50uV, lasting 2 min or more.
Results: Total 30-day mortality was 4.2% (n=32), significantly higher in women (6.7%) than men (3.2%), p=0.03. Median time to 50% ST-res did not differ in women and men (77 vs. 77.5 min), neither did maximal ST-elevation.
Women and men reaching 50% ST-res had equal (1.1 vs. 1.5%) 30-day mortality, whereas women with low-grade ST-res had significantly higher mortality (10.4 vs. 4.3%) p=0.01. Women with recurrent ischemia also were at higher risk (fig. 1). Women were older than men, this difference was less pronounced among patients with recurrent ischemia.



Conclusion: Signs of failed reperfusion or recurrence of ischemia when treating STEMI should alert us, particularly if the patient is female.

2636 Acute coronary syndromes in young premenopausal women. Is the prognosis so good?

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Background: There are few data about clinical profile and both in-hospital and long-term prognosis of acute coronary syndromes in young premenopausal women.
Methods and Results: We studied 162 consecutive women less than 55 years old (95 premenopausals and 67 postmenopausals), admitted to the cardiology department for acute chest pain in whom the diagnosis of acute myocardial infarction or unstable angina with confirmed coronary disease was finally made. Myocardial infarction was present in 69% of patients and angina in 31%. Premenopausals presented significantly more prevalence of smoking, less prevalence of hypertension, hypercholesterolemia and less extensive coronary disease than postmenopausals (18,5% vs. 39% of multivessel disease).
The onset of myocardial infarction coincided with the menstrual phase of the cycle in 48% of premenopausals (probability significantly higher than expected by choice, p=0,001).
In-hospital prognosis was good (Killip III-IV 11%, mortality rate 2.1%). Long-term follow-up was made with a median time of 40 months. Although mortality rate was low, there was a high incidence of readmissions (23% at one year in premenopausals vs 37% in postmenopausals, p=ns) being recurrent unstable angina and heart failure the most frequent causes.
Conclusions: Young premenopausal women with acute coronary syndromes have different clinical profile than young but postmenopausal ones. Most women present one vessel disease with low mortality rates but with very frequent readmissions. Temporal association between menstruation and onset of AMI was found in premenopausal patients.

PROGRESSIVE NEW STRATEGIES FOR THE TREATMENT OF MYOCARDIAL INFARCTION

2661 Autologous stem cell transplantation for myocardial regeneration in patients undergoing coronary artery bypass grafting

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Objective: Undifferentiated stem cells may be able to regenerate infarcted myocardium. Although experimental data are promising, feasibility and safety of myocardial stem cell transplantation in humans is unknown. Here, we report our initial experience with a phase-I study of human bone marrow-derived stem cell transplantation in conjunction with coronary artery bypass grafting (CABG).
Methods: Six patients (age 63 ± 7 yrs) have been enrolled in the study since July 2001. Principal inclusion criteria were: 1. acute myocardial infarction less than 3 months ago, 2. presence of a distinct area of infarcted myocardium not amenable to revascularization, 3. elective CABG operation indicated to treat ischemia of other LV wall areas, and 4. patient consent and approval by the institutional review board. Autologous, pluripotent stem cells positive for CD 133 (1 x 10E6) were isolated from the patients bone marrow aspirate one day prior to surgery, and were directly injected in the infarct border zone during the CABG operation.
Results: All patients survived the operation without major complications and have been discharged with significantly improved NYHA class. Follow-up ranges between 2 weeks and 7 months and comprises 24 patient months. Szintigraphic imaging at follow-up indicated improved myocardial perfusion in all patients, including the areas with preoperatively absent perfusion that were treated with stem cells. LV dimensions (LVEDV 149±45 vs. 137±28ml, p=0.02; LVEDV 54±4 vs.48±6mm, p=0.2) and LV ejection fraction (37±9 vs. 50±6%, p=0.05) as assessed by echocardiography have improved in all patients, as well as contractility in the previously akinetic infarct area. To date, there is no evidence of new ventricular arrhythmia or neoplasia.
Conclusion: Based on our initial experience, stem cell transplantation for myocardial regeneration can be safely performed in humans. There is evidence of improved revascularization and contractility of infarct areas, but further studies are needed to clearly determine the clinical benefit.

2662 Preliminary experience of catheter based transendocardial delivery of autologous skeletal myoblasts for cellular cardiomyoplasty

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Present therapy of heart failure after MI is focussed on medication to conserve left ventricle (LV) rest function. Cell based myocardial repair by autologous skeletal myoblasts is a novel and promising therapeutic option that has the potential to improve systolic and diastolic LV function.

Methods: Six patients, age 54±12 years (mean±std), were enrolled in this pilot safety feasibility study. All patients were symptomatic of heart failure, NYHA class 2-3, after a large Q wave anterior wall infarction. In all patients the infarct was more than 1 year ago and the residual LVEF was between 20-45%.

At baseline, a muscle biopsy was taken from the quadriceps muscle. From this muscle biopsy skeletal myoblasts were isolated and cultured for cell culture expansion. After cell culturing for 2-3 weeks, 4 patients received cellular implants in the akinetic, non-viable infarcted area by an injection catheter under fluoroscopy and NOGA guidance. On average 182 million cells (range 25-300 million), 60% myoblasts by Desmin staining (range 12-85%) were transendocardially injected by 14 injections (range 9-18) of 0.3 ml per injection.

Results: No adverse events occurred during or after the biopsy and cell transplantation procedure. All treated patients were discharged the next day after cell transplantation. To date, 6 months follow up of the first patient shows a modest improvement of LVEF by ventriculography, blood pool scintigraphy, MRI and tissue doppler imaging compared to base-line assessment. No arrythmias have been recorded. We will report on our initial experience and follow-up results in this on-going study.

2663 Thrombectomy followed by elective stent implantation in ST elevation myocardial infarction. Results from the TASMI study

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Effective myocardial reperfusion after stent implantation in patients with ST-elevation myocardial infarction (STEMI) is sometimes jeopardized by distal embolization and microvascular occlusion. Thrombus removal prior to stent implantation should reduce the risk of embolization of the thrombotic material. We report the results from a multicenter prospective registry of mechanical reperfusion in STEMI using the X-Sizer thrombus removal device followed by routine stent implantation.

Patients and methods: TASMI (Thrombectomy and Stent implantation in Myocardial Infarction) study is a prospective multicenter registry that includes patients with STEMI treated with mechanical reperfusion using the X-Sizer thrombus removal catheter system followed by routine stent implantation within 12 hours from symptoms onset. This study specially focuses on the epicardial flow and myocardial perfusion determined by the TIMI flow and Myocardial Blush Score, respectively.

Results: In 104 patients (61±9 years, 88% male) with STEMI < 12 hours from symptoms onset, thrombectomy with the X-Sizer device was attempted before stent implantation without prior balloon angioplasty. Out of them, 49% had anterior location MI. TIMI flow pre procedure was 0-1 in 74%. TIMI flow 3 post X-Sizer and before stent implantation was achieved in 69% patients. A total of 148 stents were implanted at a mean pressure of 14 atm. After stent implantation, TIMI flow 3 was obtained in 93% patients, and TIMI flow 2 in 6%. Myocardial blush 3 score was achieved in 55% of the patients at the end of the procedure. IIb/IIIa blockers were used in 14%, and the procedure was performed with the help of intraortic balloon pump implantation in 8%. During hospitalization, there were no deaths, 1 patient suffered a non-fatal reinfarction and 1 had a non disabling ischemic stroke. Outcome at 30 days after discharge was: death 0%, non-fatal reinfarction 0%, target vessel revascularization 0%, stroke 0%, and congestive heart failure 2%. Six month clinical and angiographic evaluation will be ready for presentation in August.

Conclusion: Thrombectomy using the X-Sizer device followed by routine elective stent implantation in patients with STEMI is safe and effective, with excellent clinical outcome in the TASMI study. With similar epicardial flow it seems to be able to obtain better myocardial perfusion than conventional stent implantation without prior thrombus removal. Randomized trials will determine the role of the X-Sizer Catheter System in STEMI.

2664 Comparison of immediate results of primary percutaneous coronary intervention versus facilitated percutaneous coronary intervention in acute myocardial infarction

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Primary PCI is a preferred therapy for acute myocardial infarction (MI). Adjunctive use of Gp IIb/IIIa blockers before intervention improves microvascular reperfusion. It is postulated that combination therapy of Gp IIb/IIIa blockers and half dose lytics followed by immediate PCI (Facilitated PCI) could further improve clinical outcome of patients with acute MI.

Methods: The aim of this study was to compare immediate clinical and angiographic results of treatment of consecutive non-shock patients with acute MI within 12 hrs of chest pain onset using Primary PCI (n=143; group 1) or Facilitated PCI (n=200; group 2). In group 1 pts were transferred to catheterization laboratory within 90 minutes and abciximab was given immediately before PCI at operators' discretion (48% of pts). In group 2 the transfer time to catheterization laboratory was > 90 min. All pts received i.v. bolus of 60U/kg heparin, 15 mg/35mg alteplase and abciximab at the remote hospital and were immediately transferred to angiography/PCI.

Results: there was no difference in baseline characteristics of patients in both groups. In group 1 door to needle time was 17±9 min and in group 2 remote hospital door to needle time was 158±61 min (transport time of 97±39 min). In baseline angiography TIMI 3 flow was present in 17% vs. 71% (p<0,0001), corrected TIMI frame count (cTFC) was 86±29 vs. 35±30 (p<0,0001) in group 1 and 2 respectively. Major adverse cardiac events occurred with similar frequency (death 3.5% vs. 3.5%; recurrent MI 0.7% vs 1%, rePCI 0.7% vs 1.5%; urgent bypass surgery 0% vs. 0%). However, there were 1% intracranial bleeding and 3% other severe bleeding complications in group 2. After PCI TIMI 3 flow was achieved in 93% vs. 92%, cTFC 20±12 vs. 20±13, TIMI Myocardial Perfusion Grade (MPG 3+2) in 65% vs 68% in group 1 and 2 respectively.

Conclusions: Patients after combined lytic therapy could undergo immediate PCI (Facilitated PCI) with procedural success rate similar to Primary PCI despite of substantial time delay to mechanical reperfusion. There was no differences in angiographic parameters of reperfusion after PCI despite of much higher frequency of open arteries before PCI in group 2. Bleeding complications occurred with high frequency in pts subjected to Facilitated PCI.

2665 Enoxaparin attenuates the rise in Von Willebrand factor in patients with ST-segment elevation myocardial infarction treated with fibrinolysis: results from ENTIRE-TIMI 23

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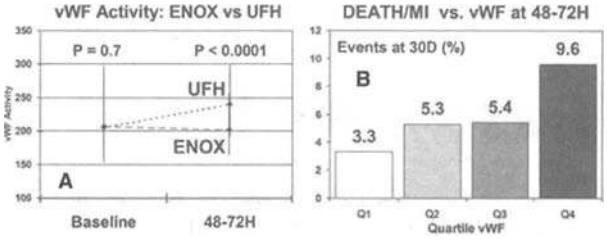
Von Willebrand Factor (vWF) is an important participant in platelet aggregation and may promote re-thrombosis early after fibrinolysis for ST-elevation MI (STEMI). Enoxaparin blunts the rise in vWF compared with unfractionated heparin (UFH) in patients (pts) with unstable angina. Little is known about the effect of enoxaparin on vWF in STEMI.

Methods: We measured vWF activity at baseline and at 48-72 hr in pts with STEMI treated with enoxaparin or UFH as adjunctive therapy for fibrinolysis (full dose TNK or 1/2-dose TNK + abciximab).

Results: Samples were available for vWF determination at both baseline and 48-72 hr in 356 pts (74%) from ENTIRE. vWF activity is presented as median [interquartile range]. Baseline vWF was similar in pts treated with UFH (202 [158-294]) vs. enoxaparin (206 [152-260]), p = 0.7). In contrast, levels of vWF at 48-72hr were higher in pts treated with UFH (240 [192-309]) compared to enoxaparin (203 [165-250], p < 0.0001, Fig A). A trend toward higher rates of death or MI was observed among patients with higher vWF activity at 48-72 hours (p-trend = 0.08) (Fig B).

Conclusions: Compared with UFH, adjunctive therapy with enoxaparin attenuates the rise in vWF activity after fibrinolysis for STEMI. This favorable effect of enoxaparin may underlie in part the reduction in death or MI observed in recent clinical trials of enoxaparin vs. UFH in STEMI.



OUTCOMES AFTER PERCUTANEOUS CORONARY INTERVENTION: THE CHALLENGE REMAINS

2677 Direct comparison of CABG and unprotected left main coronary artery stenting: immediate and medium term results

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Coronary artery bypass surgery (CABG) is currently the gold standard treatment for left main coronary artery (LMCA) disease. Recent data have demonstrated encouraging immediate and long term results of unprotected LMCA stenting (S) in selected patients. To date there has not been a clinical trial involving direct comparison between these revascularisation strategies for LMCA disease. We have evaluated the in-hospital and mid term outcome in patients with significant (> 50%) LMCA disease treated by CABG or S.

Methods and Results: Between Jan 2000 and Dec 2001, 187 consecutive patients underwent revascularization for symptomatic LMCA disease, 115 by CABG and 72 by S. Patients treated by S were at higher surgical risk: female (10.7% vs 6.4%, p=0,002), age (74±9 vs 66±9 years, p= 0.0001), renal impairment (5.3% vs 1.6%, p=0.003), impaired respiratory function (7.5% vs 2.1% p=0.0001) and clinical presentation with unstable angina (65% vs 35% p=0.014). The 2 groups were well matched in terms of diabetes (10% vs 14%, NS), previous MI (7.5% vs 8%, NS) and mean LVEF (57±14% vs 59±13%, N.S.). MACE were defined as total mortality, cardiac death, non fatal MI and target lesion revascularisation (TLR). There were 3 in hospital deaths (1 S, 2 CABG), 7 MI (4 S, 3 CABG) 2 strokes (0 S, 2 CABG). At a mean follow up of 331± 207 days there were 14 further deaths (9 S, 5 CABG, p=0.048) however, only 8 were cardiac (4 S, 4 CABG,p=NS). There were 4 cancer related deaths in the S group. The malignancy had been diagnosed prior to revascularisation in all 4 cases. There were 13 and 3 TLRs, p=0.01 respectively in the S and CABG groups. Kaplan-Meier analysis revealed cardiac death free survival at 1 year of 92±0.3% vs 91±0.3%(mean ± SEE) for S vs CABG, p=NS, and MACE free survival of 76±0.5% vs 90±0.4%, log rank p=0.02 respectively.

Conclusion: The immediate and medium term survival following unprotected LMCA stenting was equivalent to CABG. The longer term outcome of S was limited by the need for TLR. Stenting offers an excellent alternative to CABG in patients with relative contraindications to surgery.

2678 The French registry of left main coronary artery treatment

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Background: CABG is the established treatment for unprotected left main coronary artery lesions (LMCA). However, this strategy should be reconsidered in view of new refinements in PCI with stenting. As a consequence, PCI is now proposed as an alternative to CABG in some centers.

Methods: A prospective registry was set-up in 12 French high-volume centers in order to evaluate their approaches in patients with LMCA.

Results: From May to December 2001, 342 consecutive Pts were included, age 69+11years, female gender 24%, unstable angina 43%, 3 vessel disease 41%, distal LMCA 56%, EF 57±15%. Based on their demographic data, Pts were classified as good candidates for surgery in 63%, poor in 32% and contra-indicated in 5%. Treatment choice was CABG in 48%, PCI in 39% and medical in 13%. The main clinical characteristics were similar in the CABG and PCI groups except for an excess of poor candidates for surgery in the PCI group (49 vs 13%, p=0.003). Angiographic data were also similar except for more RCA lesions in the CABG group (47% vs 27%, p=0.05). Complete revascularization was achieved in 77% for CABG using 1.7±2.0 grafts (43% arterial) vs 67% for PCI (p = NS). In the PCI group, 86% of patients were pre-treated at least 3 days before with the antiplatelet association of thienopyridin and aspirin. Anti Gp2b3a were started pre-procedure in 12% and during in 6%. An intra-aortic balloon pump was inserted pre-procedure in 30%. PCI was performed via the femoral route in 92% and radial in 8% using 6 Fr guides in 69%, 7 Fr in 16% and 8 Fr in 15%. Before stent implantation, rotational atherectomy was used in 6.2% and cutting balloon in 3.1% of cases. Left main stents were deployed without predilatation in 62% of cases (1.1±0.4 stents, diameter 3.8±0.3 mm, length 11.5±3.5 mm, inflation pressure 15.1±3.1 atm.). Kissing balloon inflation was performed in distal LMCA in 55% of cases. Angiographic success was obtained in all cases. The left main MLD increased from 1.24±0.57 to 3.70±0.69 mm and % stenosis decreased from 71.1±14.1 to 6.5±9.2%. In hospital MACE were 4.8% in the CABG group including death in 4.2% (cardiac 1.8% and non cardiac 2.4%) and Q-wave-MI (0.6%) and 0.7% in the PCI group (non Q-wave-MI 0.7%, no Death, no emergency CABG). Length of stay was 14±8 days in the CABG group vs 5±3 in the PCI group (p<0.001).

Conclusion: Despite unfavorable characteristics, the PCI group for LMCA is associated with excellent in-hospital outcome and a trend towards a lower mortality rate than the CABG group. The 6-month follow-up of the entire cohort will be presented at the meeting.

2679 One-year outcomes of unprotected and protected left main stenting in the current era

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Background: Although coronary artery bypass surgery is the accepted treatment for left main coronary artery (LMCA) disease, improved coronary interventional techniques may facilitate a percutaneous approach. Data regarding patient outcomes following left main stenting remain limited.

Methods: We retrospectively reviewed outcomes among 135 consecutive patients who underwent protected or unprotected LMCA stenting at least one year prior to follow-up. Outcomes of one-year survival, myocardial infarction (MI), target-lesion revascularization (TLR), and the combined major adverse clinical event (MACE) rate were computed. Several demographic and procedural variables were tested in univariate and multivariate prediction models.

Results: Of 135 patients with a mean age of 68±10 years and mean ejection fraction 48±10%, 94(70%) underwent protected (left coronary artery grafted) and 41(30%) underwent unprotected LMCA stenting. Cardiogenic shock was present in 6% of patients. Glycoprotein 2B/3A receptor antagonists were used in 58 patients (43%). One-year clinical follow-up was obtained in 95% of patients. Survival at one year was 88% for all patients (protected 95% and unprotected 71%), TLR 21%, and the one-year MACE rate was 34%. For the 8 patients with cardiogenic shock, one-year survival was 50%. In a multivariate analysis, predictors of mortality included cardiogenic shock (odds ratio [OR] 6.0, 1.0-34.9, p=0.05) and unprotected LMCA stent (OR 3.3, 1.4-7.6, p=0.06). Congestive heart failure was a univariate predictor of survival (OR 3.3, 1.1-9.6, p=0.03). No univariate predictors of TLR were identified.

Conclusion: In the setting of protected LMCA disease, percutaneous intervention has an excellent one-year survival. Survival is reduced following unprotected LMCA stenting in a selected population felt to be poor surgical candidates. In contrast to previous outcomes analyses of patients undergoing coronary stenting, diabetes is not a predictor of left main TLR or MACE. Target-lesion revascularization for left main stents is similar to stenting of other large coronary arteries.

2680 A comparison of stenting with angioplasty for isolated stenosis of the left anterior descending coronary-artery: five-year clinical follow-up

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We have previously demonstrated that in a trial that carried out 120 symptomatic patients (pts) with isolated stenosis of the proximal left anterior descending coronary artery, primary stent implantation, as compared with balloon angioplasty (PTCA), resulted in better clinical and angiographic results at one year. The aim of this study was to establish whether the early favourable results are maintained over 5-year follow-up.

Data at five years were determined from hospital-wide clinical database. Major clinical events (death, myocardial infarction, and target lesion revascularization) were analysed according to the intention to treat analysis.

Cardiovascular mortality was significantly higher in PTCA group compared with stent group (13% vs 5%; p=0.04); myocardial infarction was not significantly different in the 2 study groups (15% vs 12%, p=0.43). In the PTCA pts, 20% underwent target lesion revascularization (TLR) versus 8% of pts in stent group (p=0.04). At five years, the event-free survival rate (80% vs 67%; p=0.05) was significantly better in stent group compared with PTCA.

Conclusions: In patients with isolated stenosis of the proximal left anterior descending coronary artery, 5-years clinical follow-up confirms a better clinical outcome in stent compared with PTCA group.

2681 Stent implatation in proximal left anterior coronary: ostial versus nonostial lesions

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Background: The presence of a left anterior descending(LAD)coronary ostial lesion poses a special management problem,since is more likely to be associated with high incidence of restenosis.
Methods: We performed an analysis between 1996 and 2001 for all patients(pts)who underwent PTCA with stent for treatment of proximal LAD disease:Group(G)I=451pts nonostial; G II=159pts ostial lesions. Demographic, clinical and angiographic fartors were similar in both groups.
Results: see table

Initial(in-cath.lab.)%	G I	G II	p-value
procedural success	98	97	NS
acute closure	0.7	0.1	NS
CABG	0.7	1.3	NS
QMI	1.0	1.3	NS
death	0.7	1.3	NS
Two-years FU%			
MACE	17	28	<0.05
TVR	10	21	<0.05

Conclusions: Coronary stenting in proximal ostial LAD lesions resulted in equivalent in-cath.lab. results when compared to proximal nonostial LAD lesions; however, the long-term FU was caracterized by higer incidence of MACE and TVR.

2682 Evaluation of different approaches to stenting true bifurcation lesions

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Background: Various approaches have been proposed for stenting true bifurcation lesions but no large studies have compared these different approaches.
Methods: The purpose of this study was to retrospectively evaluate the immediate results and mid term outcome of different approaches that were used for treating "true bifurcation lesions" (type 1) with stents. All patients had been prospectively included in a prospective single center observational database since January 1996 with 7-month follow-up and coronary angiogram in cases of clinical or stress test ischemia.
Results: Among 936 bifurcation lesions consecutively included, 474 (51%) were type 1. Patients were 64+12 yrs old, 85% male, 40% unstable angina and 10% acute MI (cardiogenic shock was excluded). A total of 1.98+0.79 vessels were dilated during the index procedure. Systematic T stenting, stenting the side branch first (Type A treatment) was used in 19% of cases. Stenting of the main branch with provisional T stenting of the side branch (Type B) was used in 74% of cases, "Culotte" stenting (type C) in 3% and others in 4%. The clinical characteristics were similar in each group. Main characteristics and results are summarized in the table below.

	Type A	Type B	Type C
Patients (n)	88	354	14
T-shape lesion (%)	33.0†	18.6	7.1
Main branch stenosis (%)	82.9±12.2†	75.1±17.0	78.8±14.1
Side branch stenosis (%)	80.7±17.5†	65.4±24.1	62.0±12.1
Main branch tubular stent (%)	72.8†	93.1	50.0*
Side branch stent (%)	100†	32.6	100*
Kissing Balloon (%)	66.3†	85.0	61.5*
Total procedure time (min)	75±15†	66±29	90±28*
In-hospital MACE (%)	8.0	4.5	35.7*
Total 7-month MACE (%)	29.3†	16.9	44.4*
Target vessel revascularization (%)	22.8†	12.8	18.2

†p<0.05 type A vs B, *p<0.05 type C vs B

Conclusion: Preliminary results of this study show that provisional T stenting of the side branch is the least time-consuming strategy associated with a lower rate of MACE and TVR compared to other strategies.

IMPACT OF THE REDEFINITION OF MYOCARDIAL INFARCTION

2683 Myocardial infarction redefined: impact of new troponin-based criteria on diagnosis and outcome of acute coronary syndromes

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Background A change from enzymatic to troponin-based diagnostic criteria for acute myocardial infarction (AMI) has been recommended by the Joint ESC/ACC Committee. This will produce parallel changes in the diagnostic frequency and risk profile of AMI, but the magnitude and direction of these changes have not been defined.
Aims To compare the diagnostic frequency and outcome of AMI according to old (CK-based) and new (troponin-based) diagnostic criteria in patients with acute coronary syndromes.
Methods 964 patients with acute coronary syndromes were studied. Serial CK and 12 hour troponin I/T concentrations were obtained, the dignostic cut-offs being 400 IU/l and 0.1 μmol/l, respectively. Rates of left ventricular failure (LVF) and hospital death were calculated according to old (CK-based) and new (troponin-based) diagnostic criteria.
Results Of the 964 patients, 297 (30.8%) fulfilled old CK criteria and 481 (49.9%) new troponin criteria for AMI. Among patients fulfilling old CK criteria, rates of ST shift and Q wave development were 79% and 77%, compared with 65% and 26% among patients fulfilling new troponin criteria. Accordingly, rates of LVF and hospital death were 22.2% and 7.4% when diagnosis was based on old CK criteria, but fell to 17.3% and 4.6% when diagnosis was based on new troponin criteria. However, when analysis was restricted to 242 patients in the upper quartile range of troponin concentrations (>=8.4 μmol/l), rates of LVF and hospital death were substantially higher (21.5% and 7.0%, p<0.001).
Conclusion Application of new troponin-based criteria increases by 62% the proportion of acute coronary syndrome patients diagnosed with AMI and simultaneously reduces the risk of LVF and hospital death by 22% and 38%, respectively. Only when the diagnosis of AMI is restricted to patients with troponin concentrations in the upper quartile range (>=0.84 μmol/l) do complication rates become comparable to those seen in patients with AMI based on old enzymatic criteria.

2684 The new definition of myocardial infarction: what does it change in the routine daily care of patients?

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Introduction: In the year 2000 the new definition of myocardial infarction has been approved and published (ESC/ACC). The aim of the present study was to analyze the clinical impact of applying this new definition.
Methods: the decisional level for myocardial infarction by using the CK-MB values was that recommended by the WHO criteria (CK-MB mass greater than 5 ng/ml), whereas the one for troponin I levels, obtained according to the suggested methodology approved by the ESC/ACC joining group, was first subjected to clinical validation at our institution and then defined at 0.13 ng/ml.
Results: In the year 2000, 760 consecutive patients were admitted for acute coronary syndrome. Of these, 359 (227 males aged 63(12) years and 132 females aged 76(11) years) had a final diagnosis of myocardial infarction with traditional criteria and 401 patients (255 males aged 64(10) years and 146 females aged 71(10) years) had a final diagnosis of unstable angina. By applying the new definition of myocardial infarction the additional number of patients with myocardial infarction was 155, with an increase of 43% compared to the classical definition. In this group of patients the use of anti-thrombotic therapy and diagnostic tools (echocardiography, exercise test, coronary angiography) was similar to that observed in the patients with non ST elevation myocardial infarction with classical criteria.
Conclusions: the new definition of myocardial infarction caused in our institution a 43% increase of this diagnosis compared to the traditional definition. The use of diagnostic resources and therapeutic strategies did not show any significant differences between patients with classical NSTEMI and with the new definition of MI. The social and economic impact of this significant increase should be carefully taken into account.

2685 The impact of redefining myocardial infarction on caseload in a large British teaching hospital

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Background: A joint European Society of Cardiology/American College of Cardiology (ESC/ACC) committee recently recommended that acute myocardial infarction (AMI) be redefined. We conducted a prospective observational study of all suspected cases of AMI admitted to a large British teachng hospital over six months, to determine the impact of applying of the new definition in practice.
Methods: A study population was assembled using the 'hot pursuit' methodology. A record of clinical features, serial electrocardiographic appearances and biomarker assay results was kept. The population was then divided into three groups by diagnostic category (1. AMI by 'traditional' modified W.H.O. criteria. 2. AMI by the 'new' ESC/ACC criteria only. 3. MI Excluded.). Each group was followed to determine rates of in-patient investigations, therapeutic interventions and outcomes.
Results: There were 1348 admissions with suspected AMI during the study period. 385 cases (28.6%) were defined as AMI by 'traditional' criteria. A further 240 cases (17.8%) of AMI were identified by the 'new' definition. Compared with patients attracting the traditional diagnosis of MI, those satisfying the new definition only were more likely to undergo in-patient coronary angiography - and revascularisation - (15.4% v 6.2%) but despite this, spent less time in hospital (mean length of stay 4.8 days v 5.8 days). In patient case fatality rate was 7.1% v 12.8%.
Conclusions: Widespread adoption of the re-definition of AMI in clinical practice will dramatically increase the number of patients labelled with the diagnosis, accompanied by, as yet, unquantified social and psychological sequelae. The additional cases make high demands for early, aggressive management; possibly leading to reduced length of hospital stay and have a relatively low early fatality rate.

2686 Prognostic implications of the new definition for non-ST-segment elevation acute myocardial infarction

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Background: A consensus document of the ESC/ACC has recently redefined acute myocardial infarction (AMI): acute coronary syndromes (ACS) with cardiac troponin (cTn) elevation but normal CK-MB levels are included in the category AMI. We evaluated the clinical and prognostic implications of this new definition.
Methods: We studied 315 patients hospitalised due to non-ST-elevation ACS and presenting cTnI elevation with or without CK-MB elevation in serial measurements performed every 6 hours during the first 24 hours after admission. Patients were divided into two groups: (1) "classic" AMI – patients presenting CK-MB elevation; (2) "redefined" AMI – typical rise and fall of cTnI with normal CK-MB levels. We compared these groups with respect to baseline clinical characteristics, in-hospital management (pharmacological therapy and myocardial revascularization procedures) and 30-day outcome (study endpoint was defined as death or re-MI occurring during the first 30 days after admission).
Results: Overall, 154 patients presented cTnI elevation with persistently normal CK-MB – "redefined" AMI – and 161 patients presented CK-MB elevation – "classic" AMI. Thus, the new definition for AMI increased the number of patients considered to have a non-ST-elevation AMI by 96%. Patients of the group "redefined" AMI were older (odds ratio 1.89; 95% IC: 1.04 - 3.44; p=0.038), less frequently treated with glycoprotein IIb/IIIa inhibitors (odds ratio 0.44; 95% IC: 0.25 - 0.77; p=0.004) and more frequently with calcium channel blockers (odds ratio 2.22; 95% IC: 1.09 - 4.53; p=0.028). The 30-day endpoint rate was 11.4% for the entire study population. Thirty-day outcome was similar for both groups of patients (11.8% endpoint rate for "classic" AMI versus 11.0% for "redefined" AMI), even after adjustment for the differences detected: the adjusted odds ratio for the 30-day risk of death or re-MI in the "redefined" AMI patients was 0.90 (95% IC: 0.44 - 1.82; ns).
Conclusion: The new AMI definition approximately doubled the number of patients having a final diagnosis of non-ST-elevation AMI. Patients considered to have positive-cTn unstable angina and those considered to have non-ST-elevation AMI, according to previous definitions, showed similar short-term outcomes. These results strengthen the importance of cTn measurements for risk stratification in patients with ACS and selection of those who may most benefit from aggressive management.

2687 Comparative outcome of chest pain unit versus coronary care unit management of acute coronary syndromes without ST-segment elevation

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Background: In patients (pts) with acute coronary syndromes without ST elevation (unstable angina, UA; non ST elevation myocardial infarction, NSTEMI) treatment with GP IIb/IIIa receptor blockers associated with early invasive strategy significantly reduce the incidence of composite coronary events (CE), but benefits vary among subsets of patients (pts). Chest pain unit (CPU) management of these pts and selection for angiography may represent an alternative solution to coronary care unit (CCU) admission.
Patients and Methods: During 2001, 142 consecutive pts (mean age 71 y, range 44-92, male 66%) with UA or NSTEMI were treated with GP IIb/IIIa antagonist in addition to standard pharmacologic therapy. Patients were randomly assigned to CPU-management(angiography depending on: recurrent angina, troponin I > 0.10 ng/l, ST-segment elevation < 0.1 mV or depression, EF < 40%) or CCU-management (early invasive strategy encouraged). Patients were followed-up for CE in-hospital and at 6 months.
Results: The two subsets of CPU-pts (n=73) and CCU-pts (n=69) shared similar baseline features, troponin levels, TIMI risk score, and presence of UA or NSTEMI on admission. PTCA was performed in 33% CPU-pts versus 49% CCU-pts (P<.05); CABG in 5.5% versus 5.8% (P=ns). Direct discharge rate was also similar (13.7% from CPU versus 14.5% from CCU; p=ns). During in-hospital stay, CPU-pts had recurrent angina, AMI and death in 29%, 4%, and 0% respectively versus 22%, 0%, and 1.4% of CCU-pts (P=ns). At 6-month follow-up, 14% CPU-pts suffered CE, versus 17% CCU-pts (P=ns). Management in CPU or in CCU did not show significant difference in CE rate (during in-hospital and at 6 months) when pts were divided in subsets according to TIMI risk score <4 (n=82) or TIMI score =/>4 (n=60).
Conclusions: Management in CPU of pts with UA and NSTEMI is a safe, effective alternative to CCU management and does not increase the likelihood of in-hospital and short-term recurrence of CE. The management is specially attractive for those hospital without availability of angiography facilities.

2688 Importance of classifying angina severity: prospective findings from the ACRE study

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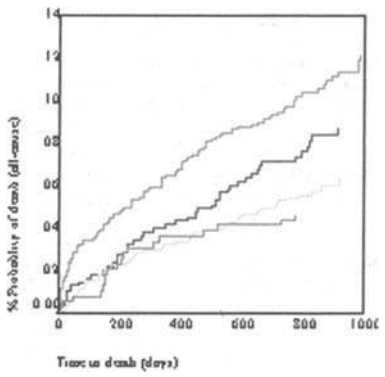
Background: Although the prevalence of angina remains high, the importance of grading angina severity is unclear. **Objective:** To determine the extent to which functional severity of angina is associated with angiographic findings, quality of life, revascularisation rates and mortality. **Design:** Prospective, population-based study with 2.5 year follow-up. Angina severity was assessed with the Canadian Cardiovascular Society (CCS) scale. **Setting:** Barts & the London NHS Trust, London, UK. **Patients:** 4020 consecutive patients undergoing coronary angiography in the Appropriateness of Coronary Revascularisation (ACRE) study. **Main outcome measures:** SF-36, Seattle Angina Questionnaire (SAQ), revascularisation rates, non-fatal myocardial infarction, mortality.
Results: Higher CCS class was linearly associated (p for linear trend <0.001) in age adjusted analyses with impaired left ventricular dysfunction, higher number of diseased vessels and worse health functioning, to a similar extent in younger and older (over 75) patients. Higher CCS class was associated with higher revascularisation rates (p <0.001; CCS IV vs I HR: 1.99, 95%CI 1.40-2.83 for angioplasty and 1.98, 1.46-2.69 for bypass graft), worse all cause mortality (p <0.001; CCS IV vs I: 1.69, 0.90-3.18) and non-fatal myocardial infarction. These effects were independent of age, sex, smoking, history of hypertension, diabetes, diseased vessels, left ventricular dysfunction and revascularisation status.
Conclusion: CCS class was linearly associated with angiographic findings, quality of life, revascularisation rates, survival and non-fatal myocardial infarction. These findings support the usefulness of grading symptomatic status among angina patients angina with this simple four level scale.



Probability of death by CCS class.

ANTIPLATELET THERAPY – RISKS AND BENEFITS

2689 Beneficial effect of a 24-48 hr "cool-down" period with tirofiban before coronary angiography in high risk patients with non-ST-segment elevation acute coronary syndromes

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Background: Recent studies show that an aggressive strategy of early angiography and revascularisation may improve outcome in high-risk non-ST elevation ACS-patients. However, only few studies have addressed the effect of timing of angiography and the effect of pre-treatment with a glycoprotein 2b/3a blocker. **Patients and Methods:** From April 2000 to Dec 2001, 220 pts with unstable angina, Braunwald class 3, with >1 mm ST depression or a positive trop T (>0.05 ng/ml) were randomised to very early (<12 hrs) angiography (group A) without 2b/3a treatment or to angiography after 24-48 hrs pre-treatment with tirofiban (group B, 0.4 μg/kg/30 min,/0.1 μg/kg/min for 24 hrs). From Jan 1,2001, tirofiban was given at a higher dose (10 μg/kg bolus/0.15 μg/kg/min) with continuation of treatment for at least 12 hrs in case PTCA was performed. Enzymatic infarct size (LDHQ48) was assessed by the area under the LDH release curve from at least 5 measurements over a period of 48 hrs. All angiography films of patients were analysed by an independent core-lab, unaware of treatment modality. **Results:** 75% of pts had elevated trop T on admission or 3 hrs thereafter. Median time to angiography was 6 (grp A) and 51 hrs (grp B). During initial hospitalisation, revascularization was performed in 75% (PTCA: 61%, CABG:14%, grp A) and 77% (PTCA: 58%, CABG: 19%, grp B) of pts.

	Group A (N=109)	Group B (N=111)	P-value
TIMI 2 or 3 pre PTCA (%)	43/65 (66)	53/65 (82)	0.04
Corr TIMI frame count post PTCA (SD)	23 (14)	18 (8)	0.05
LDHQ48 (SD)	407 (471)	242 (353)	0.004
low dose tirofiban/24 hrs	417 (443)	281 (407)	0.11
high dose tirofiban/48 hrs	398 (501)	211 (303)	0.02
negative troponin T	278 (499)	191 (260)	0.88
positive troponin T	412 (441)	257 (369)	0.004

Conclusion: An initial "cool-down" period with 24-48 hrs treatment with tirofiban is associated with a smaller enzymatic infarct size and improved angiographic outcomes, compared to immediate angiography without 2b/3a pretreatment. These benefits are more pronounced in troponin-positive patients and in pts in whom high dose tirofiban was continued until angiography.

2690 Ticlopidine and aspirin versus aspirin alone in the treatment of the acute coronary syndromes without persistent ST elevation (TICASA)

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Aggregation of platelets is the pathophysiologic basis of the acute coronary syndromes. TICASA is a polish multicenter, randomized, placebo controlled prospective trial. Rationale to the study was to use lower doses of the two antiplatelet agents acting in the two different mechanisms to improve antiplatelet action and to decrease side effect as compare with the standard doses. The aim of the study was to compare the efficacy and safety of aspirin (ASA) 100 mg with ticlopidine (TIC) 250 mg versus ASA alone in the treatment of the unstable angina. Randomization was performed in a double-blind manner by coordinating center. 454 with unstable angina were randomized to TIC 250 mg or placebo group. Intravenous heparin was to be given as a bolus dose of 5000 U followed by infusion 1000 U/h with APTT range 50-70 sec. All patients received first dose 300 mg ASA, than 100 mg per day. The primary end point was a composite of death, myocardial infarction, recurrent ischemia or hospitalization in 30 days and 3 months. The secondary end points included bleeding and other side effects. There was no difference in the base-line characteristics of the groups. A sample consisting of 454 patients in the two groups would provide the study with 80 percent power to detect a reduction of 13% (or an absolute reduction of 10 percent) of the composite end point in the 3 months incidence, assuming an event rate of 70% in the placebo group. Incidence of the components of the composite end point was not different between groups in 30 days and 3 months. The incidence of the composite end point at 30 days for the TIC group was 37,9% and for the placebo group was 43,9% (NS), at 3 months 66,9% and 76,9% (p<0,05) and 13,1% relative risk reduction. The incidence of minor and mild bleeding was similar in two groups (11,6% vs 13,4% and 4% vs 2,6%). Serious or life-threatening bleeding occurred only in TIC group - 3 patients (1,3%) but strokes only in placebo group - 3 patients (1,3%). **Conclusions:** Concomitant therapy ASA 100mg and TIC 250 mg decreased composite endpoint (death, myocardial infarction, recurrent ischemia and rehospitalization) after 3 months therapy. The treatment was safe and well tolerated.

2691 The risks versus benefits of clopidogrel treatment in acute coronary syndrome patients overall, and those undergoing CABG: the CURE trial

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Among the 12,562 ACS patients in CURE 9.3% of those randomized to clopidogrel experienced cardiovascular death, MI or stroke vs 11.4% for placebo (RR 0.80, 95% CI 0.72-0.90, <0.001). 2072 patients underwent CABG with the effects of clopidogrel being consistent with the overall benefits; 147/1011 (14.5%) clopidogrel vs 172/1061 (16.2%) placebo sustained the primary end point (RR 0.89, CI 0.71-1.11). Similar benefits were seen among the 1013 patients who underwent CABG surgery during the initial hospitalization (RR 0.78, 95%CI 0.57 -1.08). For the entire study there was a 1% excess of major bleeding but no significant excess of life threatening bleeding (2.1% clopidogrel vs 1.8% placebo, p=0.13) or haemorrhagic strokes. For those undergoing CABG a non significant excess of 1 patient per 100 experienced life threatening bleeding with clopidogrel. This apparent excess was confined to those continuing the study drug within 5 days prior to CABG (7.8% clopidogrel vs 5.0% placebo, within 7 days of CABG, RR 1.55, CI 0.93-2.57). However, there was no significant excess using the TIMI criteria for major bleeding (see table) or GUSTO criteria or severe/life threatening bleeding, even among those continuing drug within 5 days of CABG (≤5 days 3.2 vs 5.5, >5 days 2.9 vs 2.4 placebo vs clopidogrel, both ns).

CURE:Adjudicated bleeding after CABG

	Stop≤5days				Stop>5 days			
	Plac (%)	Clopid (%)	RR	95%CI	Plac (%)	Clopid %	RR	95%CI
Life threat	24(5.04)	34(7.80)	1.55	0.93-2.57	19(4.19)	17(3.73)	0.89	0.47-1.69
Other Major	6 (1.26)	8(1.83)	1.46	0.51-4.16	5(1.10)	3(0.66)	0.60	0.14-2.48
TIMI Major	13(2.73)	11(2.52)	0.92	0.42-2.04	11(2.42)	8(1.75)	0.72	0.29-1.78

Nevertheless, the more inclusive CURE criteria for major bleeding revealed 7.4% placebo vs 11.9% clopidogrel (p=0.02). The results indicate that the increase in bleeding risk with CABG is confined to those treated with clopidogrel in the preceding 5 days. Treating 1000 patients in the CURE protocol results in 28 fewer deaths, MIs or strokes in 22 patients, against an excess of 6 patients requiring transfusion and a trend for 1 patient experiencing life threatening bleeding following CABG. The excess risks of bleeding are not observed in those discontinuing clopidogrel >5days prior to surgery. Overall, these data indicate that the benefits of clopidigrel clearly outweigh the risks.

2692 Aspirin dose and bleeding events in the CURE study

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Introduction: There is limited information on the optimal dose of aspirin (ASA) in patients with acute coronary syndromes (ACS). In the CURE study, 12,562 patients with a non-ST segment elevation ACS were randomized between placebo and clopidogrel (Clop) for a mean of 9 months. Study drug was given on top of ASA, which was dosed according to local practice. The CURE protocol recommended 75-325 mg daily. In-hospital, almost all patients received heparin. We retrospectively investigated relationships between ASA dose and bleeding.

Methods: Patients were divided into 4 groups of ASA dose: <100 mg, 100-150 mg, 151-300 mg and >300 mg daily. Relative risks were adjusted for gender, weight, hypertension, TIMI risk score, angiography, percutaneous coronary intervention and bypass surgery.

Results: Adjusted rates of major or life threatening bleeding are shown below:

	Placebo		Clop		Clop/Placebo	
ASA dose (mg)	N	%	N	%	RR	95% CI
<100	19	1.92	27	2.82	1.47	0.82-2.63
100-150	64	2.24	91	3.19	1.42	1.04-1.95
151-300	46	3.32	65	4.63	1.40	0.96-2.02
>300	40	3.77	48	4.65	1.23	0.82-1.86
Adjusted p-value		0.057		0.042		

Adjusted odds ratios for highest versus lowest ASA dose groups: placebo 1.7 (95% CI 0.9-3.0), Clop group 1.5 (95% CI 0.9-2.4). There was no evidence of increasing efficacy against cardiovascular death, myocardial infarction or stroke with increasing ASA dose. The benefit of Clop was consistent across the ASA dose groups, without evidence of heterogeneity. The incidence of minor bleeding did not show a clear ASA dose response.

Conclusion: Bleeding risks with ASA are dose dependent. In order to reduce the risk of bleeding it would be prudent to use an ASA dose of 75-100 mg, especially since such patients are on multiple antithrombotic agents.

2693 Bleeding in relation to abciximab use in non ST-segment elevation acute coronary syndromes without early coronary revascularisation. Results of the GUSTO IV-ACS trial

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Treatment with the glycoprotein IIb/IIIa receptor antagonist abciximab reduces the risk of thrombotic complications, in conjunction with percutaneous coronary interventions (PCI), but also has been associated with higher bleeding rates. We investigated the bleeding risk in patients with a non ST-elevation acute coronary syndrome (NSTE-ACS) without early coronary revascularisation.

Methods and Results: In the GUSTO IV–ACS trial 24 hour or 48 hour infusion of abciximab was compared to placebo in 7800 patients with NSTE-ACS. During study drug administration 2% of the patients underwent a revascularisation procedure. A bleeding event according to the TIMI classification was seen in 1507 patients (98 major, 215 minor and 1194 insignificant). Spontaneous bleeding was seen in 911 patients. The other 596 patients had their event in conjunction with a procedure (catheterisation, PCI or CABG). However more and higher severity bleeding occurred when percutaneous coronary intervention or CABG followed catheterisation. Significant predictors for all bleeding events as found with multivariable analysis were: low molecular weight heparin (LMWH) (OR:4.9, 95%CI: 4.1-5.9), duration of abciximab infusion (OR:2.8, 95%CI: 2.3-3.3 for 24 h and (OR:3.8, 95%CI: 3.2-4.6 for 48 h infusion), region of hospitalisation (OR:4.9, 95%CI: 4.0-5.9 for patients treated in North America), inotropics given during hospitalisation (OR:3.2, 95%CI: 2.3-4.6), age over 70 years (OR:1.8, 95%CI: 1.6-2.1), female gender (OR:1.5, 95%CI: 1.3-1.7), and performance of CABG or PCI (OR:4.7, 95%CI: 1.2-19.2). Weight was not a significant predictor. The most important predictors for spontaneous bleeding in this population were the same.

Conclusions Treatment with abciximab in patients with non-ST-elevation acute coronary syndrome is, with regard to bleeding risk, safe. Major bleedings and stroke are rare. Guidelines for use of abciximab in PCI are also applicable here as well as dosing guidelines for LMWH, as many patients with NSTE-ACS will undergo an intervention and thus bleeding events associated with the intervention might be prevented.

2694 Platelet inhibition during tirofiban treatment in patients with acute coronary syndromes

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Background: early studies of GPIIb/IIIa antagonists suggest that greater than 80% receptor occupancy, with nearly complete inhibition of platelet aggregation is necessary to prevent platelet-induced coronary thrombosis. Treatment with tirofiban in acute coronary syndrome (ACS) patients reduces the risk of death, MI or refractory ischaemia at 30 days and 6 months. However, the platelet inhibitory effects of tirofiban in an ACS population remain undefined.

Methods: this is an interim analysis of 18 patients (planned total of 30) with unstable angina or non-ST-segment-elevation MI who were randomised to varying durations (24, 48, 72 and 96 hours) of tirofiban, administered as a bolus dose of 10μg/kg over 3 minutes followed by a maintenance infusion of 0.1μg/kg/min. Platelet function was measured at baseline, 6, 24, 48, 72 and 96 hours. Receptor occupancy was measured by flow cytometry (Biocytex kit). Platelet aggregation to ADP 20μM and closure time on the PFA-100 were also assessed.

Results: mean receptor occupancy on treatment was 77.5%(95%CI 74.8-80.1%). Only 30 of 55 sampling times on treatment showed receptor occupancy of > 80% and only 5 of 17 patients had > 80% receptor occupancy at all timepoints on treatment. Mean inhibition of ADP-induced platelet aggregation was 80.2% (95%CI 77.5-83.0%). Only 40 of 60 sampling times on treatment showed > 80% inhibition of platelet aggregation and only 6 of 18 patients had > 80% inhibition of platelet aggregation at all timepoints on treatment. Lower levels of receptor occupancy and inhibition of platelet aggregation were not related to a particular sampling time. Closure times on the PFA-100 correlated strongly with ADP-induced platelet aggregation (R^2=0.96), but this point-of-care assay appears overly sensitive to the inhibitory effects of GPIIb/IIIa antagonists, reaching maximum values at 60-70% inhibition of ADP-induced platelet aggregation.

Conclusion: Many ACS patients fail to achieve adequate levels of platelet inhibition while undergoing treatment with a standard regimen of tirofiban. Higher or tailored doses of tirofiban may be necessary to achieve levels of platelet inhibition that have been previously shown to optimally inhibit coronary thrombosis. In addition, the PFA-100 does not appear to be an ideal point-of-care assay for monitoring GPIIb/IIIa antagonism.

MANAGEMENT OF PATIENTS AFTER HEART TRANSPLANTATION

2695 Allograft vasculopathy surveillance and timing of coronary angiographies by tissue Doppler imaging and electron beam computed tomography

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Background: Although most transplant centers perform coronary angiograms annually for screening, these surveillance studies often fail to detect transplant coronary artery disease [TxCAD] prior to a clinical event. Routine coronary angiographies for TxCAD surveillance are also risky, especially for renal failure due to chronic renal impairment induced by cyclosporine. Thus, the non-invasive timing of coronary angiographies would be more beneficial than the recommended routine annual screening. After promising results for early TxCAD diagnosis obtained separately with pulsed-wave tissue Doppler imaging [PW-TDI] and electron beam computed tomography [EBCT], we assessed the value of both methods in combined use for TxCAD monitoring.

Methods: Throughout 18 months, 198 consecutive patients (post-transplant times: 1 -16 years) underwent PW-TDI wall motion analysis and EBCT for coronary calcification detection before coronary angiography. With PW-TDI we measured the systolic and diastolic wall motion peak velocities Sm and Em, the systolic and diastolic times TSm (from onset of first heart sound to Sm) and TEm (from onset of second heart sound to Em), and also the systolic and diastolic wall accelerations Sm/TSm and Em/TEm. Coronary calcifications were quantified by the Agatston scoring system. EBCT and PW-TDI data were tested for relationships with angiographic findings.

Results: The systolic peak velocity (Sm) and Agatston score (AS) showed the highest diagnostic values. We found significant differences (p=0.0001) between patients with and without proximal stenoses of great epicardial coronary vessels for both AS and Sm. Definite cut-off values for AS and Sm enabled highly diagnostic conclusions. The negative predictive values for relevant coronary stenoses (>50% occlusion) of Sm velocities above 9 cm/s and AS values below 50 (93.3% and 91.1% respectively) allow the exclusion of relevant stenoses in these patients. The positive predictive values for coronary stenoses of Sm and AS evaluated separately were lower. Nevertheless, using both Sm and AS together we obtained several functions that enable diagnostic decisions with probabilities of between 88 and 90%. Among these, Fishers' classification functions appeared most suitable for patient selection to coronary angiography on the basis of PW-TDI and EBCT findings.

Conclusions: Serial PW-TDI and annual EBCT are reliable for timing of cardiac catheterizations. They facilitate earlier detection of TxCAD and enable patients with a high risk for catheterization to be spared unnecessary routine angiographies.

2696 Long-term benefits of treatment with mycophenolate mofetil and low-dose cyclosporine in chronic cyclosporine induced nephrotoxicity

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Cyclosporine (CsA) induced nephrotoxicity is a major limitation in heart transplant patients (HTp). CsA dose reduction can leads to substantial early improvement in renal function. However, there aren't controlled studies that confirm if this maintenance therapy can be long term beneficial in HTp. Our aim was to study long-term benefits of therapy with low dose of CsA and mycophenolate mofetil (MMF) in HTp with CsA induced nephrotoxicity and analyze the mean related factors.

Patients and methods: Twenty-five adult HTp (mean post-HT 41.7 SD 25.7 months) were included in our retrospective analysis (22 men, mean age 58.84 SD 7.96 years.) CsA nephrotoxicity was defined as serum creatinine level (Cr) > 2 mg/dl at least in two determinations one month apart, excluding other causes of renal disease. Patients were switched from azathioprine to MMF (1-3 gr/d), followed by a stepwise reduction of CsA dosage aiming 50% of the pre-switch CsA blood level. Renal function (glomerular filtration rate (GFR) and Cr) was monitored every 3 months. Analysis of variance for repeated measures was performed for analyze renal function improvement along the time and multiple logistic regression was used to analyze variables that could be related.

Results: Mean follow-up was 30 SD 13 months (range 9-54). Results are shown in table. CsA level was the unique independent variable associated with renal function improvement (partial R^2 0.4), without influence of MMF dose, time postHT, age or sex. Renal function experimented a quickly improvement after conversion to MMF in first three months ($p < 0.001$) reaching a plateau, but without further significant improvement over the course of time.

Cyclosporine induced nephrotoxicity

	Baseline	End of follow up	p value
Cr (mg/dl)	2.37 SD 0.5	1.59 SD 0.4	< 0.0001
GFR (ml/min)	36.77 SD 10.01	54.98 SD 13.8	< 0.0001
CsA (ng/ml)	158.9 SD 69.71	85.9 SD 38	< 0.001

Cr: creatinine; GFR: glomerular filtration rate; CsA: cyclosporine; SD: standard desviation

Conclusions: CsA induced nephrotoxicity is not a progressive and irreversible disease. Reduction CsA levels and association with MMF is useful for long-term renal function improvement and could avoid terminal chronic renal failure. Unique significant factor associated with this improvement is the reduction of CsA level.

2697 Two years angiographic and clinical follow-up after coronary artery stenting in heart transplant recipients

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Cardiac allograft vasculopathy (CAV) remains the major cause of late death following heart transplantation (HT). Although the safety of coronary artery stenting in this indication has been recently reported in small series of patients, long-term follow-up data after coronary stents implantation in transplanted patients are lacking.

Methods: Since December 94, 16 patients (Pts) aged 55 ± 14 with documented severe ischemia underwent implantation of 21 coronary artery stents at a mean of 94 ± 33 months (32 to 161) after HT. Mean EF was 57 ± 9% and 13/16 Pts had multivessel disease. All Pts received aspirin (100 mg/d) and thienopyridine (for 1 month) after stenting. Quantitative coronary angiography (QCA, Phillips DCI) was performed before and after stent implantation and at a systematic 6 month angiographic control. Pts were then followed clinically every 2 months and angiographically every 12 months.

Results: 1 stent was implanted in 11 Pts and 2 stents in 5 Pts. Location of stenting was: LAD in 12 cases, LCX in 6 and RCA in 3. Indication for stenting was elective in 58%, or due to unsatisfactory acute results (16%) or restenosis (26%) after balloon angioplasty. Mean stent length was 15 ± 6 mm (7 to 34 mm). Mean balloon size was 3.0 ± 0.2 mm and mean inflation pressure was 9 ± 2 atm. Percent diameter stenosis decreased from 71 ± 14% at baseline to 26 ± 13% after stent implantation ($p<0.05$). Procedural success was 100%. At 6-month follow-up, the angiographic restenosis rate (%DS>50%) was 56% in 17/21 stents controlled. During a mean follow-up of 28 ± 24 months (2 to 86) after stent implantation, a total of 23 revascularization procedures were required in 8 Pts for in-stent restenosis or treatment of new lesions. Five/16 Pts (31%) died, 2 of non cardiac cause.

Conclusion: Coronary stenting in CAV is a palliative procedure followed by the need for multiple revascularization procedures and a high mortality rate during follow-up. However, it might remain the best therapeutic option before potential retransplantation in this life-threatened population.

2698 Is introduction of mycophenolate mofetil and reduction of cyclosporine valuable in renal dysfunction after heart transplantation? (IMPROVED-study)

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Background and Aim: Cyclosporine (CyA)-associated nephrotoxicity is a major concern in heart transplant recipients (HTR). This prospective multicenter study investigated whether introduction of the non-nephrotoxic immunosupressant mycophenolate mofetil (MMF, target level 2-4 µg/ml) after withdrawal of azathioprine (aza) followed by subsequent stepwise reduction of CyA (target level 50 ng/dl) improves impaired renal function in HTR as assessed by serial serum creatinine (Cr)-measurements. Secondary endpoints included safety and tolerability of MMF/low-dose-CyA and the influence of the initial degree of renal impairment and of comorbidity with diabetes mellitus.

Subjects: HTR >6 months pop. with Cr ≥1.7 mg/dl for ≥6 months and standard immunosuppression with CyA/aza/steroids were eligible. The treatment arm (T) included 109 and the control arm (C) 52 HTR. Study duration was 6 months.

Results: T and C did not differ in age (58.7±8.2 vs 59.5±6.6 years), sex (8% vs 11% female), pre-transplant Cr (1.3±0.5 vs 1.3±1.3 mg/dl), and Cr at time of inclusion (2.4+07 vs 2.2+06 mg/dl). During the study, Cr deceased from 2.4±0.7 to 2.1±1.0 mg/dl ($p<0.0001$) in T, but remained unchanged in C (2.2±0.6 vs 2.2±0.7 mg/dl). In the 12 months preceding the study, a negative regression slope of serial reciprocal Cr values (1/Cr) vs time indicated significant deterioration of renal function over time in both T and C. With MMF/low-dose-Cya the slope became positive in T indicating progressive renal improvement(difference of slopes: $p<0.0001$). This effect was observed in all T-subgroups (Cr 1.7-2.2, 2.3-2.8, 2.9-3.5 and, to lesser extent, >3.5 mg/dl) and in both diabetic and non-diabetic HTR. In C, the negative trend also stopped (difference of slopes: $p<0.04$). Adverse events were observed in T in 60.9% (80.0% in C; NS). 19 HTR were excluded from analysis for different reasons (2 in C). Myocardial biopsies obtained in T (not in C) at MMF/CyA target levels showed 3 rejections grade 1B, 1 grade 2, and 3 grade 3A, the latter reversible with therapy.

Conclusion: Over a wide range of Cr-levels, CyA-associated chronic nephrotoxicity in HTR proved partially reversible even in diabetics with MMF/low-dose-CyA. Long-term observation must clarify whether this renal improvement will postpone/prevent end-stage renal failure in HTR. Due to the risk of occasional moderate rejections initial graft monitoring is mandatory with this regimen. Cr-monitoring with unchanged immunosuppression did not have the same effect, but attenuated progression of renal dysfunction in the 6 month study period.

2699 Sildenafil decreases central arterial wave reflection amplitude and reduces aortic pressure and systolic stress in cardiac transplant recipients

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Objective: Cardiac transplantation is associated with increased arterial stiffness and hypertension which may contribute to cardiovascular complications. Arterial stiffening increases arterial pulse wave velocity and causes early return of reflected pressure waves to the proximal aorta from peripheral reflecting sites which augments systolic blood pressure and increases left ventricular afterload and systolic stress. The aim of this study was to determine if sildenafil, a type 5 phosphodiesterase inhibitor, influences central systolic arterial wave reflection and alters aortic blood pressure and systolic stress in cardiac transplant recipients (CTR) with stable post-transplant hypertension (HTN) taking concomitant antihypertensive medication. Methods: High-fidelity radial artery pressure waveforms were recorded non-invasively by applanation tonometry in 10 hypertensive CTR (age 55±6.0 years) and aortic pressure waveforms generated using a mathematical transfer function. Aortic augmentation index (measure of wave reflection amplitude), time delay of the reflected pressure wave and tension time index (TTI, measure of systolic stress and myocardial oxygen demand) were calculated. After baseline recordings, sildenafil (50 mg) was administrated and recordings collected every 15 minutes for 60 minutes. Results: Sildenafil influenced a significant decline in augmentation index from 7.0±12 to 0.0±13% (mean±SD, $P < 0.01$) and a delay in reflected wave travel time from 54±3.7 to 61±10 msec ($P<0.03$). Maximum modification in wave reflection occurred at 30 to 45 minutes and was associated with a decline in aortic systolic pressure from 120±8.2 to 111±8.4 mm Hg ($p<0.004$) and TTI from 2831±233 to 2630±224 mm Hg sec/min ($P<0.01$). Heart rate was 91±11 b/min at baseline and did not change with sildenafil. Conclusions: Sildenafil delays return of the reflected pressure wave from the periphery to the heart, reduces its amplitude and, therefore, decreases aortic blood pressure and systolic stress in hypertensive CTR taking other antihypertensive vasodilator medication. These changes, which are likely due to decreased arterial stiffness and pulse wave velocity, influence a decline in left ventricular afterload and myocardial oxygen demand.

2700 High rejection score is an independent predictor of cardiac allograft vasculopathy: a single center 15-year study and risk factor analysis

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Cardiac allograft vasculopathy (CAV) may represent a form of chronic allograft rejection. However, the link between acute rejection and CAV has remained elusive, as well as the relative contributions of donor and recipient immune and nonimmune risk factors as predictors of CAV.

Methods: We performed multivariate analysis of risk factors for CAV in 361 heart transplantation (HT) patients, 312 male, aged 50 ± 12 years (yrs) mean follow-up 7.2 yrs, on double or triple therapy. Rejection scores (RS) on endomyocardial biopsy were calculated (International Society for Heart and Lung Transplantation grades: 0=0; 1A=1; 1B=2; 2=3; 3A=4; 3B=5; 4=6) in the first year and during the whole follow-up. RS including only severe grades (= or >3A) were also calculated. Selective coronary angiography was performed yearly after HT and CAV onset was defined as any lesion = or >10%. The coronary tree was divided into 17 traits and a CAV severity/diffusion index was calculated for each patient summing up the scores assigned to all lesions (10% stenosis=1; 20%=2; 30%=3; 40%=4; 50%=5; 60%=6; 70%=7; 80%=8; 90%=9; 100%=10). Multivariate analysis (Cox regression) for CAV onset and severity/diffusion included: donor age, sex, and weight; recipient sex and age at HT, pre-HT diagnosis in the recipient; hypertension, diabetes and hyperlipidemia post-HT; number of treated rejections and RS at 1st year and total; immunosuppressive drug dosage (mg/Kg) at 3, 6, 12 months (mo).

Results: Overall survival post HT was 84%, 75% and 62% at 1, 5, and 10 yrs. The incidence of CAV (Kaplan-Meier) was 2% at 1 year, 22% at 5 and 39% at 10 yrs. Multivariate analysis showed, as risk factors for CAV onset, older (>32 yrs) donor age ($p<0.0001$, RR=9.9), male donor sex ($p<0.001$, RR=3.2), high (>0.15) RS for severe grades ($p<0.02$, RR=2.01), high Cyclosporin at 3 mo ($p<0.02$, RR=1.9). Risk factors for CAV severity/diffusion were higher (>68 Kg) donor weight ($p<0.01$, RR=7.5), high prednisone dosage at 1 yr ($p<0.0001$, RR=21.1), ischemic heart disease pre-HT ($p<0.002$, RR=9.7).

Conclusions: High rejection score was an independent predictor for CAV onset, as well as known risk factors such as older donor age and male sex. Predictors of CAV severity/diffusion were mainly non immune features. This strongly suggests an immune-mediated basis for CAV onset as well as non-immune modulation of CAV progression.

BETA BLOCKER THERAPY IN HEART FAILURE: CURRENT THOUGHTS

2701 Randomized comparison on the effects of metoprolol or carvedilol on myocardial substrate utilization in chronic heart failure

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Background: The benefits of beta-blocker therapy in congestive heart failure (CHF) is well documented. Surprisingly, the pathophysiological basis for this benefit is not clearly established. Evidence from animal models of CHF suggests that therapy with beta-blockers can improve cardiac efficiency and energy substrate utilization by reducing cardiac free fatty acid (FFA) utilization and increasing cardiac lactate consumption. Furthermore, it is possible that selective versus nonselective beta-blockers have differential impacts on cardiac metabolism

Methods: This was a randomized, double blind study, designed to compare the effects of 4 months of therapy with metoprolol versus carvedilol on myocardial substrate utilization in patients with CHF. After randomization, patients were instrumented with Swan-Ganz, coronary sinus, and arterial catheters for measurement of hemodynamics and myocardial FFA and lactate extraction. Patients were then started on a beta-blocker and up-titrated to 50mg bid of metoprolol or 25mg bid of carvedilol. After 4 months of therapy, hemodynamics and transcardiac substrate extraction measurements were repeated.

Results: Eleven patients (age 54 ± 3yrs, LVEF 18 ± 2%) were randomized to carvedilol and 11 patients (age 54 ± 4yrs, LVEF 21 ± 3%) were randomized to metoprolol. Neither drug caused a significant change in cardiac filling pressures, mean arterial pressure, or cardiac index. Both drugs caused a significant reduction in heart rate (-8 ± 3 bpm metoprolol; -16 ± 3 bpm carvedilol; $P < 0.05$ vs baseline for both). Carvedilol caused a significant reduction in FFA extraction (0.12 ± 0.02 mmol/L vs 0.1 ± 0.02 mmol/L, $P < 0.05$) and tended to increase lactate extraction (0.24 ± 0.05mmol/L vs 0.35 ± 0.08mmol/L, $P < 0.08$)

By contrast, metoprolol caused no change in FFA extraction (0.09 ± 0.02mmol/L vs 0.11 ± 0.03 mmol/L, P = NS) and caused a significant reduction in lactate extraction (0.18 ± 0.03 mmol/L vs 0.11 ± 0.04mmol/L, $P < 0.05$).

Conclusion: Chronic carvedilol therapy in CHF patients had a beneficial effect on myocardial substrate extraction with a shift from FFA to lactate utilization. This shift could lead to an improvement in myocardial efficiency in carvedilol treated patients compared to those treated with metoprolol. The clinical significance of these differential effects awaits the results of randomized clinical trials

2702 Effect of beta-blockade on activation of the renin-angiotensin-aldosterone system in chronic heart failure

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Background: Beta-blockers are known to suppress renin release in hypertension and lower levels in patients taking ACEIs. However, it is not entirely clear what is the effect of additional beta-blockade on renin and aldosterone levels in severe heart failure (HF) patients taking ACEIs over the longer term. It has been postulated that beta-blockers may obviate the need for ACEIs in heart failure or reduce their effectiveness.

Methods: 49 pts with chronic HF were given metoprolol 50mg bd or carvedilol 25mg bd (50%) after a 4 week dose titration period in addition to standard therapy with diuretics and ACEIs in a prospective trial. Samples for plasma rennin activity (PRA), and aldosterone were taken at baseline, 4, 12 and 52 weeks after starting therapy.

Results: Treatment with either beta-blocker significantly lowered PRA at 4 weeks compared to baseline (-2.0±0.6 nmol/L/hr, p=0.006), but at 12 weeks this had reduced to -1.1±0.6 nmol/L/hr (p=0.08), and at 52 weeks PRA was not significantly different from baseline (+1.05±0.6 nmol/L/hr, p=0.13). Aldosterone levels did not change significantly from baseline at 4 or12 weeks although there was a non-significant trend for lower levels at 52 weeks(aldo baseline 232 ±154 pmol/L, 52 weeks 192±100 pmol/L, p=0.09). There were no sig difference between metoprolol and carvedilol.

Conclusions: these results indicate that the suppressive effect of beta-blockers on plasma renin activity in HF pts already on an ACEI is temporary and there is no significant effect on serum aldosterone levels. Therefore patients on beta-blockers still need to continue with an ACEI or ARB as well as an aldosterone antagonist.

2703 Efficacy of bisoprolol, β1-selective adrenoblocker, in chronic heart failure patients with increased cytokine level

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Activation of cytokine system may develop in the patients with chronic heart failure (CHF). TNFa is one of the biochemical markers of this state. In order to investigate pharmacological effects of b-adrenoblockers as neurohomonal-modulating agents in CHF with increased cytokine level, we performed an open randomized comparative trial.

Methods: 38 male CHF patients with increased TNFa level aged under 60, II-IV NYHA functional classes (FC), ejection fraction (EF) <30% received 24-weeks treatment with either traditional pharmacotherapy of CHF with ACE inhibitors (2nd group) or the same with 10 mg o.d. bisoprolol, b1-selective adrenoblocker,(1st group). We evaluated NYHA FC, hemodynamic state (heart rate (HR), blood pressure (BP) level), heart morphofunctional parameters (end systolic and diastolic volume (ESV, EDV), EF), exercise capacity and TNFa plasma level.

Results: The NYHA FC was diminished more significantly in the 1st group pts. It was decreased from 3.5+0.53 to 2.25+0.46 ($p<0.001$) in the 1st gr and from 3.43+0.53 to 2.57+0.98 ($p<0.01$) in the 2nd one. The best beneficial influence on hemodynamic, morphofunctional parameters and exercise capacity was more significantly in the 1st gr too (the results are in the table).

Changes in hemodynamic parameters

	HR, %	SBP, %	DBP, %	ESV, %	EDV, %	EF, %
1 group	- 22.6**	-13.6**	-14.5**	-16.6**	-8.3*	+17.7**
2 group	-6.1*	-8.3*	-4.26*	-8.4*	-3.7	+9.7*

* - $p<0.01$; ** - $p<0.001$ compared with baseline

Exercise capacity (EC) increased from 27.5+10.35 Wt to 47.5+18.32 Wt ($p<0.0001$) in the 1st group and from 25.7+9.76 to 31.43+15.74 Wt ($p<0.01$) in the 2nd one. The TNFa plasma level diminished from 12.37+6.00 to 2.24+1.28 pg.ml-1 ($p<0.0001$) in the 1st group and from 14.88+8.77 to 6.3+3.8 pg.ml-1 ($p<0.005$) in the 2nd one.

In conclusion, the addition of bisoprolol to traditional pharmacotherapy of CHF in the patients with increased cytokine level significantly improves the quality of life, left ventricular function, hemodynamic parameters and exercise capacity. All these changes were accompanied with the decreasing of TNFa plasma level.

2704 Effect of carvedilol on major clinical events in patients with severe heart failure and an extremely depressed ejection fraction

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Background: Despite the demonstrated survival benefit of beta-blockers in heart failure (HF), many physicians avoid the use of these drugs in patients with extremely depressed LV function in the belief that they will not respond favorably or may be adversely affected by treatment.

Methods: Of the 2289 patients with severe HF enrolled in the COPERNICUS trial, 371 patients had a baseline LV ejection fraction ≤ 15%. These patients had a lower mean systolic blood pressure (117 vs 125 mm Hg) and were more likely to be treated with digitalis (73% vs 65%) than patients with higher EF (both $P<0.002$) but were otherwise similar in their baseline characteristics. Both subgroups of patients were randomized to placebo (PBO) or carvedilol (CRV) for up to 29 months.

Results: Shown below are 1-year Kaplan-Meier rates and risk reductions with CRV (Cox model). The effects of CRV on all-cause mortality and on the risks of death or hospitalization (for any reason or for a specific cause) in patients with EF ≤ 15% were similar to those seen in patients with higher EF. CRV reduced the risk of permanent discontinuation of study drug in patients with EF ≤ 15% (by 32%) and in those with higher EF (by 19%).

Conclusion: CRV is effective and well tolerated even in patients with severe HF symptoms and an extreme depression of LV systolic function.

	Ejection fraction ≤ 15%			Ejection fraction > 15%		
	PBO (n=191)	CRV (n=180)	Change in risk	PBO (n=942)	CRV (n=976)	Change in risk
All-cause mortality	23.8%	18.9%	-30%	17.4%	9.7%	-36%
Death or hospitalization for worsening HF	46.3%	30.3%	-39%	36.0%	24.6%	-28%
Death or cardiovascular hospitalization	52.1%	34.6%	-41%	39.4%	29.4%	-23%
Death or any hospitalization	59.9%	47.2%	-33%	50.7%	40.4%	-21%

2705 Patients with dilated cardiomyopathy with attenuated elevation of cardiac sympathetic activity are poor responder to carvedilol therapy

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Because reverse remodeling by carvedilol lasts for at least one year, non-responders to carvedilol determined at 4 months after its administration can belong to the responders determined at one year. We studied the charcteristics of responders and non-responders to investigate the mechanism of left ventricular reverse remodeling. One hundred and eighteen patients (pts) with dilated cardiomyopathy were enrolled. Before, at 4 months and 1 year after the onset of carvedilol (20mg/day) therapy, cardiac function (left ventricular ejection fraction (EF) determined by radionuclide ventriculography), cardiac sympathetic nerve activity (cSNA), and plasma brain natriuretic peptide (BNP) concentrations were determined. cSNA was assessed by myocardial uptake of metaiodobenzylguanidine (MIBG) calculated as the heart/mediastinal activity ratio (H/M). Storage and release of MIBG was also calculated as percent myocardial MIBG washout rate (WR). Low H/M or high WR suggests the enhanced cSNA. Responders were defined as the patients with improved EF by more than 5 units. Baseline EF (26±10 vs 26±8%), plasma BNP concentrations (158±163 vs 163±159pg/ml), and early H/M before carvedilol therapy did not differ between the non-responders (29pts) and responders (63pts) determined at 4 months. However, the baseline value for delayed H/M of non-responders was larger (2.06±0.44 vs 1.88±0.35) and WR was smaller (43.1±12.2 vs 49.5±11.2%) than those of the responders. Baseline value for EF of non-responders (10pts) determined at 1 year was slightly larger (32±8 vs 25±9%), BNP was smaller (64±47 vs 171±176pg/ml), delayed H/M was larger (2.40±0.48 vs 1.93±0.36), and WR was further smaller (39.1±9.5 vs 48.4±11.8%) than those of the responders (47pts). Conclusions: Patients with dilated cardiomyopathy and attenuated elevation of both baseline cSNA and BNP may receive less benefit from reverse remodeling by carvedilol therapy.

2706 Prescription rate and safety of betablockers in heart failure patients with or without diabetes

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Background: Physicians are still concerned to prescribe beta-blockers (BB) in diabetic patients (pts).

Methods: We evaluated the applicability, the safety profile, and the outcome of BB use in pts with heart failure (HF) enrolled in an outcomes research study, planned by the Italian Association of Hospital Cardiologists (ANMCO). Pts were followed-up for 1 year. During 1 month, 3091 pts were enrolled by 202 Cardiological centres: 25% of the recruited pts were already on BB treatment, 28% started treatment at the enrolment visit, and 47% were not started on BB. The present analysis refers to the pts with complete 1 year follow-up (96.5%).

Results: Diabetic pts (21.8%) were older (66±9 vs 63±12 yrs; $p<0.0001$), with a higher prevalence of female (33 vs 25%; $p=0.001$), they had higher NYHA class (III-IV: 38 vs 33%; $p<0.01$), and mean heart rate (80±14 vs 77±15 bpm; $p<0.0001$) than pts without diabetes. No difference of mean EF was observed between the two groups. A lower rate of pts with diabetes was already on BB at enrolment visit (23 vs 27%; $p<0.05$), however the same rate of diabetic and non-diabetic pts started BB during the study. Adverse reactions leading to BB permanent discontinuation were not significantly different in diabetic and non-diabetic pts (26.5% vs 22.7%, NS). The overall 1-year mortality for the total population and split by BB use and diabetes is shows in the table.

1-year mortality	BB	No BB	RR [95%CI]	Total
Total population	8%	17%	2.17 [1.76-2.67]	12%
Diabetic	11%	21%	2.26 [1.77-2.90]	16%
Non-diabetic	7%	16%	1.87 [1.28-2.79]	11%

The Cox multivariate analysis showed that advanced age, NYHA class III-IV, higher heart rate, lower systolic blood pressure, EF < 30% and diabetes are independent risk factors for 1-year mortality, while the use of BB was a protective factor in both diabetics and non-diabetics.

Conclusions: This outcomes research study showed that: - BB were largely prescribed in HF pts with or without diabetes; - the safety and tolerability profile of BB was similar in diabetics and non-diabetics; - the relative reduction of 1-year survival and hospitalisation rates obtained by BB was similar in pts with or without diabetes. Therefore, to deny BB treatment to diabetic pts is not reasonable.

NEW DEVELOPMENTS IN THREE-DIMENSIONAL ECHOCARDIOGRAPHY

2726 Left ventricular remodelling after myocardial infarction assessed by 3D echocardiography

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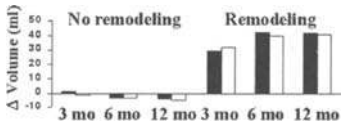
Background: Left ventricular (LV) volumes, assessed by 3 D echocardiography (3DE) are 2 to 3 times more accurate compared to 2 D echocardiography. Therefore serial individual changes in LV volume can be measured more accurately.
Aim: Accurate assessment of LV remodeling after myocardial infarction (MI) using 3DE.
Methods: 3DE was obtained prospectively in 32 consecutive patients post MI, starting at 5 ± 3 days after the event (baseline), and at 3, 6 and 12 months. The TomTec Freehand® method in conjunction with an ATL 5000®, were used with second harmonic imaging, using the apical window. LV volumes were measured off-line with TomTec Echo-Scan® software. Remodeling was defined as an end-diastolic volume (EDV) or end-systolic volume (ESV) increase of > 10% from baseline.
Results: 18 non-remodelers and 14 remodelers could be identified. Baseline EDV, ESV and ejection fraction (EF) were, respectively, 95.2 ± 25.2 ml, 54.5 ± 19.4 ml, and 43.6 ± 7.7% in the non-remodelers, and 94.8 ± 25.8 ml, 57.5 ± 18.8 ml, and 40.7 ± 7.9% in the remodelers. At 12 months EDV, ESV and EF were respectively 92.1 ± 28.9 ml, 48.7 ± 20.2, and 48.0 ± 6.9% (p = NS for all) in the non-remodelers, and 137.2 ± 56.7 ml (p = 0.001), 87.4 ± 49.6 ml (p = 0.007), and 40.3 ± 13.2% (p = NS)in the remodelers. In this group there was no significant increase (delta) in volumes after 3 months (see figure; black = EDV, white = ESV).



Change in volume (ml) from baseline.

Conclusions: 3 DE can accurately discriminate between non-remodelers and remodelers after MI. In the former there was no significant volume or EF change during the entire follow-up of 12 months, whilst in the latter there was a significant volume increase from baseline to 3 months, without a significant increase thereafter.

2727 Analysis of regional left ventricular endocardial wall area. A novel free hand three-dimensional Doppler tissue imaging parameter in coronary artery disease

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The assessment of regional left ventricular (LV) wall function using Doppler tissue imaging (DTI) is a promising new technique, yet its quantitation is one-dimensional and its diplay transmural only. Furthermore 70% of regional myocardial contraction occurs at the level of the endocardium, which currently can only be imaged as a cross-section by pulsed Doppler and 2-D DTI.
We thus hypothesized, that free-hand three-dimensional (3-D) DTI is feasible and reveals qualitative and quantitative information about the function of a whole endocardial wall area, a novel parameter for the assessment of regional LV function. We also hypothesized, that differences can be seen between normal and hypokinetic wall segments in patients with coronary artery disease.
Method: 18 patients with coronary artery disease (8 f, 10 m, age 60 ± 16, EF 58 ± 14%) were imaged with two-dimensional Color DTI using a Sequoia echo unit interfaced with a free-hand 3-D (TomTec) system. The endocardial surfaces of the basal and mid lateral and septal left ventricular wall segments were reconstructed in 3-D. Segmental 3-D DTI velocities of the endocardial areas were measured throughout the cardiac cycle and compared with the standard 2-D gray scale (ASE) wall motion score by two independent observers using qualitative visual assessment.
Results: Color 3-D DTI velocity patterns of endocardial wall areas were reconstructed (n=146 total). In normal wall segments (n=90) the velocity patterns of the 3-D endocardial area were more homogeneously distributed than in hypokinetic wall segments (n=56). Peak (mean) systolic velocities were 1.14 ± 0.44 mm/sec (0.37 ± 0.17); peak (mean) diastolic velocities were - 1.66 ± 0.98 mm/sec (-0.51 ± 0.28) respectively. There was a strong correlation between peak systolic and diastolic 3-D endocardial wall area velocities (y = 0.62x + 0.72, r = 0.71, p = 0.0002) and between systolic wall acceleration of the endocardial 3D DTI area and 2-D gray scale wall motion score (r = 0.8, p = 0.007).
Conclusions: 1) Free-hand 3-D Color Doppler tissue imaging is feasible and provides endocardial wall area velocities as well as velocity patterns. 2) Qualitative and quantitative differences between the motion patterns of the endocardial area of normal and hypokinetic left ventricular wall segments can be identified. 3) 3-D free hand DTI may have the potential to provide new insights into regional LV wall function and thus may provide a new technique for the diagnosis of coronary artery disease.

2728 Left ventricular volume measurements with and without Optison for left ventricular opacification – The "endocardial wall" concept revisited

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Background In two- and three-dimensional echocardiography, left ventricular (LV) volumes are measured by contour tracing of the innermost endocardial border. The ultrasound contrast agent Optison ® is used for improvement of LV endocardial definition. By filling up intertrabecular space it delineates the outermost endocardial border. This filling up and the "blooming" effect might increase LV volume measurements.
Aim To compare LV volume measurements with and without Optison infusion for LV opacification.
Methods Twenty coronary artery disease patients with a good apical acoustic window underwent transthoracic three-dimensional echocardiography using the TomTec Freehand ® method with and without continuous Optison infusion. Optison was given intravenously as a 0,2-0,3 ml bolus followed by 25 ml/hr continuous infusion. Infusion speed was adjusted to yield complete LV opacification, which could be maintained for 4-6 minutes. As a carrier liquid, 0,9% NaCl was used at an infusion speed of 200 ml/hr. Second harmonic gray-scale tissue imaging with normal (baseline) and low (Optison) mechanical index was used in all patients, and ultrasound machine settings were optimized for endocardial border delineation. LV volumes were measured off-line with TomTec Echo-Scan ® software.
Results For values of end-diastolic (EDV) and end-systolic (ESV) volumes, stroke volume (SV), and ejection fraction (EF) at baseline and during Optison infusion, see table (values expressed as mean ± 1SD, in ml or %).

	Baseline	Optison	p-value
EDV	109,2 ± 33,2	142,1 ± 53,4	0,001
ESV	65,8 ± 30,1	87,9 ± 44,6	0,002
SV	43,2 ± 11,5	54,2 ± 20,4	0,018
EF	41,8 ± 12,1	39,9 ± 14,7	0,499

Conclusions Optison causes a significant increase in LV volume, but not EF measurements compared to baseline. Intertrabecular space appears to be a substantial part of the LV cavity. Therefore, the "endocardial wall" concept should be redefined.

2729 Accelerated three-dimensional echocardiographic protocols for left ventricular volume quantification: comparison of quadriplane and octaplane mode

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Background: Long-axis based quantification (quadriplane and octaplane 3-dimensional echocardiography, Q3D, O3D) is feasible and accurate method of ejection fraction (EF) measurement in unselected routine patients, providing significantly better correlation with MUGA than 2-dimensional echocardiography. We aimed to assess the impact of different acquisition protocols upon Q3D/O3D quantification of LV volumes and EF using multiple gated radionuclide angiography (MUGA) as a reference.
Methods: 28 unselected patients referred for routine assessment of LV function (pts) were studied (5F,23M; age 56±9, BSA 1.93±.19m^2, no image quality criteria). Transthoracic two-dimensional echocardiography (2D) was performed using Toshiba Powervision 7000 and Tomtec Echoview was used for rotational acquisition of datasets for Q3D and O3D from the apical window at 3° and 10° interval. LV volumes were quantified by tracing in 4 (Q3D) or 8 (O3D) coaxial long axis cutplanes.
Results: Volumes could be calculated by 3D echocardiography (3DE) in 28/28 pts. Mean EF was 54±20% in MUGA and 48±17%, 49±17%, 49±18% and 49±18% in 3°O3D, 3°Q3D, 10°O3D, 10°Q3D, resp. (p<0.001 vs. MUGA). 3DE provided excellent correlation of WEF values with MUGA (r=0.92-0.93, similar for all modes). There were no differences between 4 modes of 3D regarding endsystolic and enddiastolic volumes (ANOVA p>0.05) as well as observer variability. The reproducibility of any 3DE method in unselected group was worse than that of MUGA and similar in the 4 approaches (Pearson's r 0.91-0.92 for EF and 0.98-0.99 for volumes). There was a twofold reduction of acquisition time between 3° vs 10° and, independently, analysis time between O3D and Q3D.
Conclusions: Quadriplane analysis of 3-dimensional echocardiography acquired at 10 degree interval provides optimal workload-to-accuracy relationship regarding the quantification of left ventricular volumes and ejection fraction using radionuclide values as a reference.

2730 Three-dimensional echocardiographic wall motion is related to haemodynamic improvement during invasive testing in resynchronization therapy

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Background: Three-dimensional echocardiography (3-D-Echo) provides a quantitative assessment of left ventricular regional wall motion. Patients under resynchronization therapy demonstrate different patterns of regional wall motion in sinus rhythm and in the optimal pacing mode.
Methods: In 12 patients with chronic heart failure on resynchronization therapy differences of changes of partial volumes between sinus rhythm and optimized pacing mode were compared. 13-24 volumes per heart cycle were acquired by transoesophageal 3-D-Echo (HP-Sonos 5500/TOMTEC). Endocardial surfaces were generated by a validated automatical technique (thin plate spline model TOMTEC). Each volume was cut into 8 slices, each slice was subdivided into 6 segments resulting in a total of 48 regions. Cyclic changes of the partial volumes segments were evaluated quantitatively (MATLAB script). The number of dyskinetic segments and the regional ejection fraction in hypokinetic segments were evaluated. The changes of these parameters between sinus rhythm and optimized pacing mode were compared to respective changes in pulse pressure and dP/dt max at initial invasive testing.
Results: The number of dyskinetic segments decreased in 10/12 patients during optimized pacing as compared to sinus rhythm from a median value of 9 to a median value of 4-5. This decrease correlated significantly with percent increase of pulse pressure (r=0.64) and dP/dt max (r=0.48). There was a minor but significant increase of regional ejection fraction in hypokinetic segments in 6/12 patients without significant correlation with hemodynamic improvement.
Conclusion: The reduction of dyskinetic segments correlates with hemodynamic improvement and seems to be the major effect of resynchronisation therapy. Echocardiographic three-dimensional regional wall motion analysis provides a tool to study the effects of electrical therapy on the pattern of ventricular contraction.

2731 Experimental results and first human experiences with an interventional closing device of the left atrial apendage (PLAATO)

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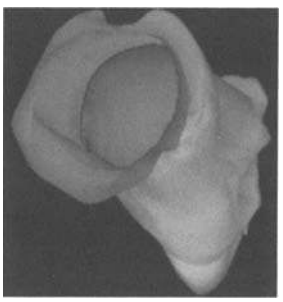
Background: Transesophageal echocardiography (TEE) is the method of choice for evaluating the left atrial appendage (LAA). However, complete morphological analysis of the LAA is often difficult due to its anatomical variability and trabeculation. This prospective study thought to determine experimentally, whether threedimensional (3D) TEE allows accurate determination of the volume and morphology of the LAA and hence may facilitate the human implantation of a LAA occlusion device in patients with atrial fibrillation.
Methods: The LAA was reconstructed in 17 pig hearts using 3D TEE (EchoPAC-3D®). Then, LAA casts were obtained (Technovit 7143®). The casts and 3D TEE results were compared with respect to volume, number of lobuli and main trabeculae (diameter > 5 mm). In addition, six 3D TEE reconstructions of the LAA were performed prior to and after interventional occlusion of the LAA with the PLAATOTM device.
Results: There was no difference in 3D-TEE reconstructed and cast determined volumes (R = 0,96; 95% KI 0,88 – 0,98). The quantity of lobuli was correctly determined by 3D TEE. The amount of main trabeculae was correctly obtained in 14 of 17 cases. 3D TEE allowed exact determination of the ostial diameter of the LAA in those patients who underwent interventional occlusion of the LAA. In addition, the complete occlusion of the LAA was demonstrated by 3D TEE in all cases.



Conclusions: 3D transesophageal echocardiographic reconstruction of the left atrial appendage allows accurate determination of the volume and morphology of the appendage and recognition of accessory lobuli and prominent trabeculae. In addition, the technique facilitates the implantation of a left atrial appendage occlusion device.

EUROPEAN SOCIETY OF CARDIOLOGY LECTURE ON POPULATION SCIENCES

2733 West of Scotland Coronary Prevention study (WOSCOPS): 5-year post-trial follow-up

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Background & Methods: WOSCOPS recruits were followed for 5 years after trial completion for assessment of the long-term benefits and safety of within-trial treatment with pravastatin. Subjects were withdrawn from study medication at trial closure, and returned to their general practitioners for lipid management. All deaths were recorded and adjudicated for cause.
Results: The Table shows the numbers of deaths in the 5-year post-trial follow-up and overall post-randomisation. P-values and hazard ratios (HR) for each mortality outcome were calculated from the log-rank test and Cox proportional hazards regression models comparing randomised treatment groups.

Cause of death	Pravastatin Post-trial	n=3302 Overall	Placebo Post-trial	n=3293 Overall	P (Log-rank)	HR (95% CI)
CV	92	142	113	186	0.010	0.75(0.60, 0.94)
Non-CV	130	186	134	196	0.505	0.93(0.76, 1.14)
All Cause	222	328	247	382	0.025	0.85(0.73,0.98)
Cancer	105	149	101	150	0.847	0.98(0.78,1.23)

WOSCOPS: 5 Year Post Study Mortality

Conclusions: Non-cardiovascular (CV) and cancer mortality were balanced between treatment groups throughout. The post-trial follow-up reinforces the benefits of pravastatin treatment on CV and all-cause mortality, with absolute risk reductions post-trial similar to those within-trial.

2734 Nutritional habits among subjects with cardiovascular risk factors

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Background Diet is an underestimated therapeutic means for the management of cardiovascular risk factors particularly because of an insufficient knowledge concerning dietary habits of non insulin dependent diabetic (HG), hypercholesterolemic (HTC) and hypertensive (HBP) subjects. However, drug therapy effectiveness could be improved by the use of an appropriate diet. Dietary data were analysed for males participants in the cross-sectional nutritional survey carried out from 1995 to 1997 in three French regions Lille, Strasbourg and Toulouse.
Methods A sample of 1100 men aged 45-64 years was randomly drawn from electoral rolls. Subjects were screened for cardiovascular risk factors in a medical health centre and a 3-day food intake record was set up. HTC, HG and HBP subjects were defined as follows: total cholesterol >=6.2 mmol/l or drug therapy, glycemia >=7.8 mmol/l or drug therapy and systolic >=160 or diastolic blood pressure >=95 mmHg or drug therapy. Each risk factor was analysed separately and after taking into account these three risk factors together, a risk score was built and three groups were identified: 0 risk (group1), 1 risk (group2), and 2 or 3 risks (group3). Recorded energy intake was validated (EI) using the ratio between recorded energy intake and estimated basal metabolic rate (BMR). The statistical significance of the comparisons between groups for cardiovascular risk factors was assessed by ANOVA analysis with adjustment for confounders: age, educational level, centre, body mass index, tobacco consumption and physical activity.
Results Total energy intake and energy without alcohol were reduced by about 10% in the third group (2329/2074 kcal/d) when compared to group 1 (2577/2386 kcal/d) and the trend was significant. The proportion of energy supplied by carbohydrate was 42.6%, 42.2% and 40.7% in groups 1, 2 and 3 respectively ($p<0.05$). Globally, the proportion of energy supplied by carbohydrate was lower and energy coming from fat or protein was higher when one risk factor was prevalent whatever the type of risk factor. The proportion of calories from alcohol was 30% higher in group 3 vs group 1 ($p<0.001$). When subjects with EI/BMR ratio <1.05 were excluded from the analysis, the majority of the differences observed were not modified substantially.
Conclusion Among subjects with one or more cardiovascular risk factors nutritional habits were worse than among subjects with no risk factor and were not in agreement with classical dietary recommendations.

2735 Clinical and angiographic differences between smokers and non-smokers after successful thrombolysis: insights from the APRICOT trials

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Background: In patients treated with thrombolysis for acute myocardial infarction (MI) a paradoxical beneficial outcome has been reported in smokers. This benefit was thought to be related to younger age, less severe coronary disease and a better response to thrombolytic therapy. In the subset of patients with successful thrombolysis clinical outcome is strongly related to reocclusion of the infarct related artery. The current analysis sought to identify clinical and angiographic baseline-characteristics in smokers, and tried to assess whether smoking status is associated with reocclusion.
Methods: In the Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis trials (APRICOT-1 and APRICOT-2) 335 consecutive patients < 71 years had thrombolysis for acute myocardial infarction within 4 hours of symptom onset and a patent infarct artery at angiography < 48 hours. In APRICOT- 1 (1987-1991) patients were randomized to aspirin 325 mg (n=87) or Coumadin (INR 2.8-4.0, n=72), in APRICOT-2 (1995-2000) to aspirin 80 mg (n=78) or aspirin 80 mg in combination with Coumadin (INR 2-3, n=98). Three-month follow-up angiography was performed to assess the patency status of the infarct artery.
Results: At baseline 68% (227/335) of patients were current smokers. Smokers were younger (53.3 9 versus 57.3 8, p< 0.01) and had less often a history of previous infarction (5% versus 17%, p< 0.01) than non-smokers. Enzymatic infarct size did not differ: maximum creatine kinase 1549 1657 versus 1239 1082, p=ns. At baseline angiography smokers had more often single vessel disease (62% versus 46%, p < 0.01) and smooth infarct lesions (68% versus 54%, p = 0.02). Reocclusion rates were 15% (34/227) in smokers as compared to 25% (27/108) in non-smokers (OR 0.53 (95% CI 0.29-0.97, p = 0.03). At multivariate analysis smoking was strongly associated with sustained patency of the infarct artery: OR 0.54 (0.28-1.03, p=.06).
Conclusions: Clinical and angiographic characteristics observed in smokers in the MI population at large also seem to apply to smokers after successful thrombolysis. However, in the APRICOT-patients smoking status appears to remain an important predictor of beneficial outcome, even after correction for baseline characteristics.

NEW ULTRASOUND TECHNIQUES TO UNDERSTAND CARDIOVASCULAR FUNCTION

2740 How useful is valve resistance for the distinction between true severe stenosis and "pseudostenosis" in low flow – Low gradient aortic stenosis

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Background: Although we and others have shown that - in contrast to previous suggestions - aortic valve resistance (R) is flow dependent, the question whether R is of value for the distinction between true severe stenosis and "pseudostenosis" (functionally small aortic valve area [AVA]) in patients with aortic stenosis (AS) who present with small AVA but low flow and low gradient remains controversial.
Methods: To evaluate the value of R in this particular setting, models of stenotic aortic valves without doming (plates), models of doming valves (nozzles) and biological stenotic valves with various degrees of stenosis severity and extensible orifices were studied in a pulsatile in-vitro circuit using Doppler ultrasound and direct pressure and flow measurement. Anatomic AVA ranged from 0.5 to 1.25 cm^2 and cardiac output was varied from 2.0 to 8.9 l/min. R (dynes s cm^{-5}) was calculated as 1333 × mean transvalvular pressure gradient × ejection time/stroke volume. Effective orifice areas (EOA) were calculated with the continuity equation. Orifices of the biological stenotic valves were recorded with a high-speed video camera for AVA planimetry. Valves with EOA < 0.85cm^2 and mean gradients between 10 and 40 mmHg at low cardiac output (<3.5L/min) were divided into 2 groups. Group A = true severe stenosis: EOA remained < 0.85cm^2 at normal flow. Group B = pseudostenosis: increase of EOA beyond 0.85cm^2 at normal flow.
Results: R was significantly smaller in pseudostenosis as compared to true severe stenosis (129±28 vs 176±33 120 dynes s cm^{-5}; p< 0.001) even when baseline AVA did not significantly differ between groups. However, there was a wide overlap that did not allow the clear distinction between the two entities on the absis of an individual R value in the majority of settings. Nevertheless, R of < 120 dynes s cm^{-5} accurately identified nonsevere stenosis. When subgroups of A and B without significant difference in gradient were compared, R was no longer significantly different between group A and B (162±26 vs 141±22; p=.08).
Conclusions: Valve resistance is not only flow-dependent, it is also of limited value for the distinction between true severe stenosis and pseudostenosis in the setting of aortic stenosis with small AVA but low flow and low gradient. Only a very low R of < 120 dynes s cm^{-5} accurately identifies pseudostenosis. In most instances, procedures that attempt to normalize flow and repeat AVA calculations such as dobutamine echocardiography will be necessary for correct diagnosis.

2741 A new index based on an automated segmental motion analysis system in the evaluation of aortic stenosis severity

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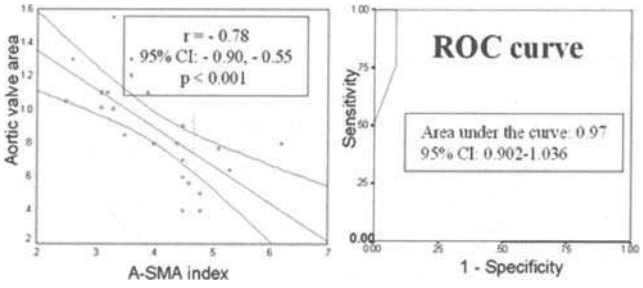
A slowered left ventricular contraction has been described in patients with aortic stenosis (AS). The aim of this study was to evaluate the possible role of a new Automated segmental motion analysis system in the assessment of AS severity.
Twenty-two patients with AS, sinus rhythm, and normal left ventricular ejection fraction were prospectively studied. All patients underwent two echocardiographic studies by two differente blinded investigators: 1) Conventional Doppler measurements: transaortic gradients, aortic valve area (continuity equation); 2) Automated Segmental Motion Analysis (ASMA, Aloka, Japan). This system automatically detect endocardial borders and quantitatively displays fractional area changes of left ventricular cavity in real time. An index (A-index) was calculated by dividing the time from the R wave of the ECG to the maximal area shortenning by the RR interval.
Results: (see figure) There was a significant strong negative correlation between the aortic valve area and A-index (r = -0.78; 95% confidence interval: -0.90, -0.55; p < 0.001). The area under the receiving operator characteristic curve in the diagnosis of severe AS was very high (0.97; 95% confidence interval: 0.90-1.0). An A-index of > 0.40 showed a sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy for the diagnosis of severe AS of 100%, 91.7%, 92.3%, 100%, and 95.8%, respectively.



A-SMA index and aortic stenosis.

Conclusion: this new index based on an automated segmental motion analysis system is allows an easy evaluation of AS severity, showing a strong correlation with aortic valve area and a very high accuracy in the diagnosis of severe AS.

2742 Temporal changes in post systolic thickening during prolonged ischaemia quantified by ultrasound deformation imaging in a closed-chest pig model

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Study aim: To define the precise sequence of temporal changes in Post Systolic Thickening (PST) induced by a 90 minute total PTCA balloon coronary artery occlusion (CAO) as measured by ultrasonic deformation imaging.
Background: PST has been proposed as a clinical marker of viability in ischemic segments. Little information is available on the time course of changes in PST as total CAO progresses to acute transmural infarction.
Methods: In 6 pigs, basal posterior wall radial deformation data was acquired pre- and 1-, 5-, 30-, 60-, and 90 min after total circumflex CAO. High temporal and spatial resolution data sets were obtained at 5 MHz in M-mode RF-data format (Toshiba Powervision 6000). Customized software was used to extract strain rate and strain (S). Simultaneous LV pressures were recorded (Millar-catheter). Aortic valve closure (AVC) was defined to be 20 msec before peak negative dp/dt. End-systolic S, max S after AVC and their timings were measured. PST-Index (PSTI) was calculated from these measurements as the relation between max S and end-systolic S. Infarction was confirmed by TTC-staining.
Results: End-systolic S decreased significantly during CAO ($p<0.001$ vs baseline). Increased PSTI was found in all ischemic segments at all stages of CAO ($p<0.05$ vs baseline). The PSTI peaked at 5 min CAO then tended to decline. There was no increase in time to max S nor a change in the duration of systole. Moreover, EF based on Teichholz, remained constant after an initial small drop at 1 min CAO and thus did not bias regional S estimates.

	S End-Systole (%)	S max after AVC (%)	PST-Index (%)	EF (%)
Baseline	39 ± 12	39 ± 12	2 ± 4	59 ± 16
Occ. 1min	19 ± 10	31 ± 13	89 ± 41 *	42 ± 11 *
Occ. 5min	12 ± 5 *	21 ± 4 *	111 ± 93 *	39 ± 14
Occ. 30 min	12 ± 6 *	21 ± 4 *	79 ± 44 *	39 ± 8 *
Occ. 60 min	10 ± 7 *	19 ± 4 *	50 ± 41	42 ± 9
Occ. 90min	10 ± 7 *	19 ± 10 *	95 ± 15 *	40 ± 17

*$p<0.05$ vs baseline

Conclusion: An increase in PSTI occurs instantly in ischemic segments following CAO. PSTI then decreases with duration of ischemia. Time to max S is not affected by ischemia duration. To use PST as a marker of viability it is essential to integrate PSTI data with that of changes in end-systolic S.

2743 The non-invasive differentiation of chronic nontransmural versus transmural myocardial infarction by ultrasonic strain rate imaging

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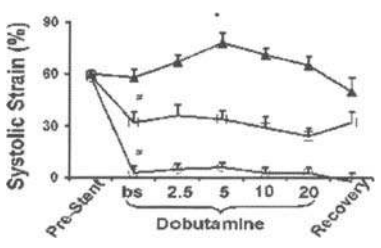
Background: In a correlative functional/histopathological study we sought to investigate whether the measurement of induced changes in regional ultrasonic strain profiles could reliably differentiate chronic nontransmural from transmural myocardial infarction.
Methods and Results: After implantation of a stenosing copper-coated stent to produce marked endothelial proliferation in the circumflex artery, a series of pigs were followed over a 5-week period. Post-sacrifice histology studies showed 10 to have developed a nontransmural and 8 a transmural myocardial infarction. Eight additional animals, without stent implantation, were enrolled to serve as a control group. Changes in regional radial function were monitored by measuring systolic strain pre-stent implantation and at 5 weeks, at baseline (bs) and during an incremental dobutamine infusion. In the control group, the dobutamine infusion induced an initial increase of strain at low dose dobutamine (bs=58±5%, at 5 μg/kg/min=78±6%; $p<0.05$) but a subsequent decrease during higher infusion rates with a return at peak infusion to bs values. In the nontransmural infarct group, baseline strain were significantly lower compared to pre-stent values (32±6%, $p<0.05$). During the dobutamine infusion, strain showed no change but postsystolic thickening increased significantly. The transmural myocardial infarction group showed almost no measurable strain in the posterior wall at dobutamine bs (3±4%; $p<0.0001$ vs pre-stent) and there was no further change during the incremental dobutamine infusion (at 20 μg/kg/min:3±3%; p=NS vs bs).
Conclusions: In the experimental setting, the regional ultrasonic strain response to a dobutamine infusion can clearly differentiate chronic nontransmural from transmural myocardial infarction.



Non-transmural vs transmural infarction.

2744 Can the ultrasonic comets announce the presence of extravascular lung water?

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Background: The "comet-tail" is an ultrasound sign detectable with cardiac ultrasound instrument on the chest, and consisting of multiple comet-tails fanning out from the lung surface. It originates from water-thickened interlobular septa. Portable echocardiographic systems would be ideal for non-radiological bedside assessment of extravascular lung water.
Aim: to assess the feasibility and value of ultrasonic comet sign.
Methods: We studied 38 consecutive in-hospital patients (11 females, age 61±14 years) admitted in cardiological intensive care unit, with a portable cardiac echo system (Optigo, Agilent Technologies, 2.5 MHz transducer). In each patient, we scanned by echo the chest (right and left hemithorax, from second to fourth intercostal space,from parasternal to midaxillary line) and the presence of comet-sign was noted by observers blinded to clinical diagnosis. An individual patient comet echo score was obtained by summing the number of comets (from 0 to 4) in each of the scanning spaces. On the same day, the patients underwent a chest X ray, with specific assessment of extravascular lung water by two pneumologist-radiologists blinded to clinical and echo findings. Radiological lung water score ranged from 0 (no interstitial water) to 50 (marked increase in water); this previously validated score incorporated assessment of hilar vessels (dimension, density, blurring), Kerley lines (A, B and C), micronoduli, widening of interlobar fissures, peribronchial and perivascular cuffs, subpleural effusion, and diffuse increase in density.
Results: The chest ultrasound scan was obtained in all patients (feasibility= 100%). The imaging time per examination was always <3 minutes. The Comet sign was found in 8/28 patients without and 10/10 patients with radiological signs of extravascular lung water (interstitial in 5, alveolar in 5). The Comet echo score was higher in the 5 patients with alveolar when compared to the 5 with only interstitial lung water (39±20 vs 17±8, $p< 0.06$). There was a linear correlation between echo comet score and radiological lung water score ($r=0.69$, $p<0.001$).
Conclusion: The Comet-tail is a simple, non time-consuming and reasonably accurate chest ultrasound sign of extravascular lung water which can be obtained at bedside with portable echo equipment and is not restricted by cardiac acoustic window limitations.

COMPUTER DEMONSTRATION

2746 G8 cardio-ANMCO: a common, national computerized program for echocardiogram archiving and reporting

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Availability of a common computerized program for echo archiving and reporting at national and/or international level could make possible to standardize the echo report between different echo-labs, and to use the wealth of data obtainable with echocardiography, and to exploit its capillary territorial distribution to collect echo data in a standard format for epidemiologic, scientific and administrative purposes. Therefore, an ad hoc joint Italian Society of Cardiology, and Italian Society of Echocardiography task force worked in conjunction with Italian branch of Agilent Technology to standardize the phraseology of accepted echo terms and of the quantitative parameters derived from transthoracic and transesophageal echo examination at rest as well as during exercise and pharmacological stress, and to develop an ad hoc software. This echo archiving and reporting program is part of the whole G8-CARDIO-ANMCO software project addressed to standardize and computerize the whole cardiological chart. The software was developed by Agilent Technology to provide a fast, easy-access, easy to use report generator for the non-computer specialist using Oracle 7.0 database and Power Builder 5.0 to develop a user-friendly interface. Between July and September 2001, the program was tested by 22 echo-labs throughout Italy selected for not being involved in the software analysis and development. Test was carried out using predefined standardized forms and qualitative evaluation of 4 software characteristics. The number of reports databased was 2464 for resting echo (reporting time= 8±3 min), and 273 for stress echo (reporting time= 10±5 min). Resting echo software characteristics analysis results were: thoroughness (complete 40%, rather complete 60%, incomplete 0%, inadequate 0%), user-friendliness (very easy 13%, easy 67%, difficult 20%, unusable 0%), graphic-look (very nice 7%, nice 80%, misleading 13%, difficult 0%), final report (adequate 67%, too long 7%, difficult-to-read 13%, inadequate 13%). Stress echo software characteristics analysis results were: thoroughness (complete 45%, rather complete 36%, incomplete 18%, inadequate 0%), user-friendliness (very easy 18%, easy 73%, difficult 9%, unusable 0%), graphic-look (very nice 18%, nice 73%, misleading 9%, difficult 0%), final report (adequate 73%, too long 18%, difficult-to-read 0%, inadequate 9%).

To our knowledge this software represents the first experience of a common computerized programme for echo archiving and reporting carried out at national level.

2747 EchoAnalyzer: software for the analysis of three- and four- dimensional echocardiographic data

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Purpose: For improved visualization of 3- and 4-dimensional (3D/4D) echocardiographic data sets a major issue is the capability of performing interactive measurements. Some of the techniques already described are not yet available for clinical routine due to the lack of appropriate, integrated software. Our purpose was to develop a new system that can provide visualization and quantification of 3D/4D echocardiographic data sets.

Methods: We have developed an echocardiographic analysis system - called EchoAnalyzer - integrating many up-to-date visualization and quantification methods. The EchoAnalyzer analysis software is developed in C++ using the GUI library Qt (Trolltech, Oslo, Norway) and runs on all 32-bit Windows systems and on all major Unix derivatives including Linux. The performance of an up-to-date low-cost PC is sufficient for all visualization and quantification methods described in the following.

Results: The EchoAnalyzer system provides color-coded, interactive 3D/4D volume visualization, measurements of cavity volumes, ejection fraction and cardiac output, regurgitation quantification and display of flow profiles.

The visualized volume can be interactively rotated and clipping planes can be used to mask the parts of the volume that obstruct the view on the structures of interest.

The difficult task of the segmentation for the determination of the ejection fraction was solved by the integration of a nearly automatic segmentation algorithm. This reduces the user time and enables the user to correct segmentation results if necessary.

Cardiac output measurements can be performed with EchoAnalyzer either by segmentation of the left ventricle or by spherical surface integration of velocity vectors (SIVV).

To quantify regurgitation, a method was implemented which yields reliable volumetric measurements also for asymmetrical, wall-impinging regurgitation jets. Velocity landscapes have been developed for visualization and quantification of blood flow. After definition of the primary direction of flow by the user an angle correction of the velocity component is performed and the result is displayed as a 3D profile plot, which can be rotated interactively.

Conclusion: The presented EchoAnalyzer software enables visualization and quantification of three-/four-dimensional echocardiographic data sets. It integrates several recently developed methods into a user-friendly environment, making them available for routine clinical medicine.

POSTER DISPLAY V

MODERATED POSTER SESSION V

P2748 Tissue Doppler echocardiography: the new method of right ventricle preload assessment in patients with atrial septal defect

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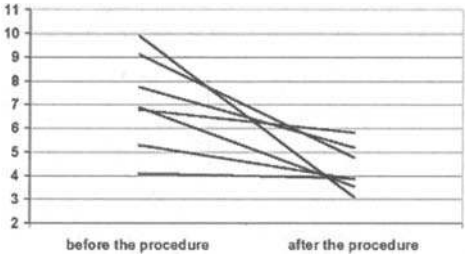
Introduction: Recently the new method of left ventricle preload assessment based on tissue doppler echocardiography was described. The maximal early diastolic mitral inflow velocity (E) depends on diastolic compliance of left ventricle and left ventricle preload. The maximal early diastolic velocity of mitral annulus assessed by tissue doppler (Ea) depends only on diastolic compliance of left ventricle. Thus, E/Ea ratio represents left ventricle preload. To assess right ventricle preload by E/Ea ratio, E should represent maximal early diastolic tricuspid inflow velocity and Ea should represent maximal early diastolic velocity of tricuspid annulus.

Aim of the study: To assess right ventricle preload in patients with atrial septal defect (ASD) by E/Ea ratio before and after closure of the defect.

Material and methods: In 7 patients (5 females, 2 males) aged 19-60 years (mean age 42.6) ASD was diagnosed by transesophageal echocardiography. The diameters of the defects were 9-14mm (mean diameter 12.4mm). In all the patients maximal early diastolic tricuspid inflow velocity (E) and maximal eary diastolic velocity of tricuspid annulus (Ea) were calculated. The measurements were done before and after the percutaneous closure of the defects by Amplatzer devices.

Results: Significant decrease of E/Ea ratio after the procedure was observed. The E/Ea ratio decreased from 6.65±2.25 to 4.27±0.93 ($p<0.01$).



Conclusion: Significant decrease of E/Ea ratio was observed after the closure of ASD. E/Ea ratio seems to be useful noninvasive method for right ventricle preload assessment.

P2749 The C825T-polymorphism of GNB3 gene is associated with reduced expression of IK,ACh mRNA in patients with coronary artery disease

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Stimulation of muscarinic receptors activates the G-protein-regulated inward rectifying potassium current (IK,ACh), the major effector of cholinergic stimulation in atrial myocytes. We recently showed that homozygous 825T-allele carriers of the GNB3 gene exhibit larger density of the background inward rectifier current IK1 but reduced activation of IK,ACh. Here we studied whether the observed current changes are due to alterations mRNA levels of the main IK1 transcript Kir2.1 and those of the IK,ACh transcripts GIRK1 (Kir3.1) and GIRK4 (Kir3.4). Differences in mRNA levels of respective channel subunits were evaluated by competitive RT-PCR in right atrial biopsies from patients with coronary artery disease but without rhythm disturbances. To quantify the target mRNA concentrations, internal RNA competitors (mimics) containing the respective specific primers flanking a part of the coding sequence for cardiac alpha-actin were used to quantify the mRNA levels of respective channel subunit. The GNB3 genotype of the patients was determined in peripheral blood by PCR and restriction analysis. The mRNA concentrations of the IK1 transcript Kir2.1 was not different between the three genotype groups (23.6±3.7 fmol/μg RNA, n=8, TT-genotype vs. 19.2±2.4 fmol/μg RNA, n=5, CC-genotype and 21.1±2.2 fmol/μg RNA, n=7, CT-genotype, respectively (mean±SEM; n.s.). On the other hand, the mRNA concentration of GIRK4 was significantly smaller in homozygous 825T-allele carriers when compared to the two other genotype groups: 5.4±0.6 fmol/μg RNA, n=12, TT-genotype vs. 11.9±0.9 fmol/μg RNA, n=15, CC-genotype and 12.2±0.4 fmol/μg RNA, n=9, CT-genotype, respectively ($P<0.05$). Similar significant differences were detected for the mRNA levels of GIRK1. Our data point to a genetically fixed transcriptional down-regulation of IK,ACh in homozygous 825T-allele carriers. The reduced channel expression may be interpreted as an adaptation mechanism to the enhanced G-protein-mediated signal transduction in these subjects.

P2750 Role of endothelin in metabolic regulation of coronary blood flow

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Coronary metabolic dilation is likely mediated by the production of a myriad of vasodilators. However, withdrawal of vasoconstrictors may also play a role in this process, because the titration of production of constrictors and dilators may confer finer and quicker regulation of myocardial perfusion. Because endothelin-1 (ET) is a potent vasoconstrictor and is produced in the heart, we hypothesized that ET-induced constriction decreases during augmented metabolic demands. To test this hypothesis instrumented swine (n=7) were studied while running on a treadmill (0-5 km/h) before and after ETA antagonism (ETA) and non-specific ET receptor antagonism (ETAB). ETA and ETAB decreased myocardial oxygen extraction at rest and to a lesser extent during exercise, thereby shifting the relation between myocardial oxygen supply and demand upward. The effect of ETA was significantly larger than that of ETAB. In conclusion, ET has a tonic constrictor influence through the ETA receptor at rest, but its constrictor influence is decreased during increased myocardial metabolism. Stimulation of the ETB receptor exerts a tonic vasodilator influence that partially counteracts the effect of ET on the ETA receptor.

P2751 Correlation of pacing "stress" NOGA mapping with SPECT for diagnosis of myocardial ischaemia

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Background: Biosense NOGA Electromechanical mapping (EMM) has been shown to identify viable myocardium but not to reliably distinguish between normal and ischemic regions of the Left Ventricle. Since Linear Local Shortening (LLS) is a validated measurement of myocardial mechanical function we postulated that the findings of LLS obtained during active stress would reflect a worsening in mechanical function that could identify areas of ischemic myocardium. In the present study EMM was performed at rest and with atrial pacing (stress) and subsequently compared to rest/stress SPECT.

Methods: EMM at rest and during atrial pacing at 85% of MPHR was performed in 16 patients (pts) (256 segments) and matched to SPECT imaging (99Tc-sestamibi).Both methods were displayed in a 16-segment bull's eye. A T-test was used to compare means and SD of rest and paced LLS values within each perfusion group and a comparative analysis between the four perfusion groups regarding LLS values was performed by ANOVA in both rest and paced states. A $P< 0.05$ was considered significant.

Results: The table shows values for LLS at rest and with atrial pacing according to the results of the perfusion studies. The differences between normal and reversible segments and normal and non-reversible segments with little residual activity (scar) were significant ($p<0.05$).

SPECT(No. Segments)	Rest LLS%	Paced LLS %
Normal (n=151)	15.0±8.7(a)	11.3±8.7(e)
Reversible(n=49)	12.3±6.5(b)	7.3±5.9(f)
Non-reversible viable(n=26)	11.9±5.2(c)	8.6±5.0(g)
Non-reversible scar (n=30)	10.9±6.9(d)	5.4±6.5(h)

$p<0.05$- T-test: a vs. e, b vs f, c vs g, d vs h. ANOVA: e vs. f, e vs.h

Discussion: This study describes the first pacing stress model for EMM. A uniform response to atrial pacing characterized by a drop in LLS is noted but is significantly greater in ischemic myocardium compared to normal myocardium. Areas of non-reversible scar type perfusion defects demonstrate even greater deterioration in LLS. Thus, this is the first evidence that Pacing "Stress" EMM allows for the characterization of ischemic myocardial segments. Further studies with larger sample sizes need to be performed to confirm the present findings.

P2752 Pacing "stress" electromechanical mapping: detecting myocardial viability in SPECT non-reversible perfusion defects

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Background: Upcoming studies using stem cells incorporate electromechanical mapping (EMM) to guide local myocardial treatment. Therefore, EMM has to accurately identify viable myocardium.Prior studies have shown good correlation between EMM and SPECT perfusion imaging in identifying reversible vs. non-reversible defects according to Unipolar Voltage (UniV) values. Non-reversible defects however may retain significant residual tracer activity after resting injection (viable) as opposed to very little residual activity (scar). Given the above, we postulated that "stress" EMM technique could be useful to identify areas of viability with more precision than could previously be achieved with resting maps.

Methods: EMM at rest and during atrial pacing at 85% of MPHR was performed in 16 patients (pts) (256 segments) and matched to SPECT imaging (99Tc-sestamibi).Both methods were displayed in a 16-segment bull's eye. A T-test was used to compare means and SD of rest and paced UniV values within each perfusion group and a comparative analysis between the four perfusion groups regarding UniV values was performed by ANOVA in both rest and paced states. A $P< 0.05$ was considered significant.

Results: The table shows values for UniV at rest and with atrial pacing according to the results of the perfusion studies.

SPECT(No.Segments)	Rest UniV (mV)	Paced UniV (mV)
Normal(n=151)	17.9±5.1(a)	24.8±7.6(e)
Reversible(n=49)	16.3±4.5(b)	23.3±8.0(f)
Non-reversible Viable(n=26)	13.0±5.0(c)	22.1±9.0(g)
Non-reversible Scar(n=30)	10.5±3.0(d)	14.4±5.4(h)

$P<0.05$- T-test: a vs. e, b vs f, c vs. g, d vs h.ANOVA: a vs. c, a vs. d, b vs. d, h vs. e, h vs. f, h vs. g.

Discussion: Pacing "stress" EMM describes a generalized increase in UniV associated with atrial pacing. However, voltage values during stress cannot be utilized to diagnose myocardial ischemia. Moreover, "stress" electromechanical map is able to further identify viable myocardium in areas where a non-reversible perfusion defect is present by SPECT imaging, which cannot be accomplished by resting maps. "Stress" EMM may play a role in the precise guidance of direct myocardial injection therapies though future studies with larger sample sizes need to be performed to confirm the present results.

P2753 Does microbubble destruction influence the assessment of contrast replenishment kinetics using power pulse inversion imaging?

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In contrast echocardiography microbubble replenishment kinetics (RKs) allow the assessment of blood volume (parameter A) and mean microbubble velocity (parameter β) using the exponential function f(t)=A*(1-exp(-β*t)). The new imaging technique Power Pulse Inversion (PPI) allows real-time imaging of echocontrast agents, however, bubble destruction might occur even at lowest emission power. We therefore assessed the impact of the emission power on bubble destruction and on the fitting parameters using a hard- and a soft shell echo-contrast agent. Methods: In a capillary flow phantom mimicking microcirculation, blood flow was varied from 10-45 ml/min which corresponded to flow velocities between 2 and 9 mm/s. During constant infusion of Definity (BMS Medical Imaging) and AF0150 (Alliance Pharmaceutical Corp.), real-time PPI imaging (20Hz) was performed at variable emission power (MI = 0.09-0.39) using an HDI 5000 (ATL). For both agents, bubble destruction was calculated at all emission power levels. RKs following ultrasound-induced destruction of microbubbles were assessed at the same emission powers. The parameters A and β were calculated using the fitting function described above. Results: 1) No significant bubble destruction was observed using Definity at MIs < 0.13 and AF0150 at MIs < 0.11. At higher emission powers, the PPI signal intensity dropped significantly indicating the presence of bubble destruction ($p < 0.001$). Higher degrees of bubble destruction were observed at lower flow velocities. 2) Using Definity at MIs < 0.13 and AF0150 at MIs < 0.11 no significant differences were found for the slopes of the β/flow and A*β/flow regression curves. However, higher emission power levels caused a significant decrease of absolute β values and of the slopes of the β/flow and A*β/flow regression curves ($p < 0.001$). Conclusion: At low emission powers, PPI allows non-destructive real-time imaging of Definity and AF0150 microbubbles. Bubble destruction at higher emission power levels could cause 1) a decrease of PPI intensity resulting in an underestimation of regional blood volume and 2) changes in the β/flow relationship resulting in underestimation of regional flow velocity. Thus, to adequately assess absolute or relative changes in regional blood volume and mean microbubble velocity, non-destructive real-time imaging might be a prerequisite.

P2754 Systemic adenovirus-mediated gene transfer of human GTP cyclohydrolase-1 increases liver, plasma and aortic tetrahydrobiopterin levels in mice

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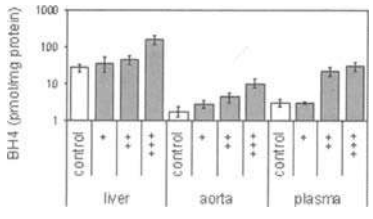
Background Reduced NO bioavailability due to endothelial nitric oxide synthase (eNOS) dysfunction is a feature of vascular disease. Tetrahydrobiopterin (BH4) is a required co-factor for NO production by eNOS, but the relationship between plasma and intracellular endothelial BH4 levels in the regulation of eNOS function remains unclear. To investigate the utility of gene transfer to increase BH4 levels in vivo, we aimed to augment plasma and vascular BH4 levels in mice by systemic gene transfer of human GTP cyclohydrolase-1 (GTPCH), the rate-limiting enzyme in BH4 biosynthesis.

Methods We constructed a recombinant adenovirus (Ad.GTPCH) encoding human GTPCH cDNA linked to the HA epitope. 5×10^8 (+) 5×10^9 (++) or 5×10^{10} (+++) virus particles of Ad.GTPCH or Ad.GFP (control) were injected into tail veins of 24 week old C57Bl6 mice (n=3 per group). Organs were harvested for analysis after 5 days. Expression of recombinant GTPCH protein was assessed by immunohistochemistry and Western blotting. BH4 levels were measured using differential iodine oxidation and HPLC.

Results We observed high level recombinant GTPCH expression in liver 5 days after gene transfer. GTPCH gene transfer markedly increased BH4 levels in liver, plasma and aorta compared to controls, in a dose-dependent fashion (Figure).



Conclusion Systemic adenovirus-mediated gene transfer of GTPCH in mice is a promising in vivo model to investigate modulation of eNOS dysfunction by systemically increased BH4 in vascular disease.

P2755 Assessment of circumferential-radial shear strains in normal and ischaemic myocardium based on ultrasonic strain/strain rate imaging

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Background: Until now ultrasonic strain(S) and strain rate(SR) estimates have measured one-dimensional strain (either radial or longitudinal) to quantify regional myocardial deformation. However, to quantify three-dimensional deformation one needs to resolve the complete strain tensor, including shear strains, as the latter describe torsion and local twisting/untwisting. Shear deformation develops gradually during systole but is a dominant and very fast event in the opposite direction during isovolumic relaxation (IVR). In magnetic resonance tagging (MR) studies circumferential-radial shear strain has already been shown to be of clinical relevance in patients with aortic stenosis.

Study Aims: To determine if circumferential-radial shear strain (CRSS) could be measured during the isovolumic relaxation period by a modification of the ultrasonic SR/S technique.

Methods: High frame rate (>200 f.p.s)/Color Doppler Myocardial velocity data sets (parasternal short axis view at a midpapillary muscle level) were acquired in 11 young normals and in 6 patients with regional ischemic septal hypokinesia. CRSS rates (CRS SR) were extracted off-line using custom-made software and were estimated as the lateral gradient of the axial velocity. CRSS was obtained as a temporal integral of the CRS SR. The CRSS describes the epi- to endocardial torsion. For statistical analysis the non-parametric Mann-Whitney test was used.

Results: From 34 acquired segments, 3 (8%) were rejected from analysis due to low signal-to-noise ratio. In normals during IVR the maximal CRS SR value for the septum was 0.553±0.20 1/s and for lateral wall was -0.723±0.45 1/s. CRSS in IVR was -2.79±1.0% in the lateral wall and 2.98±1.7% in the septum. These values corelate well with the normal CRSS values previously obtained by MR. In patients all measured values were significantly lower both in septum (maximal CRSSR: 0.148±0.11/s**; CRSS: 0.7±0.1%*) and in the lateral wall (maximal CRSSR: -0.307±0.28 1/s**; CRSS: 1.15±1.02*) compare to normals, *p<0.02,**p<0.01.

Conclusions: In conclusion, CRSS can be calculated from a high temporal resolution CDMI velocity data set. Initial clinical findings have shown this technique can identify and quantify normal segmental values and can quantify abnormal regional CRSS related to segmental disease.

P2756 Molecular mechanisms of short-term electrical remodelling in a rabbit model of rapid atrial pacing

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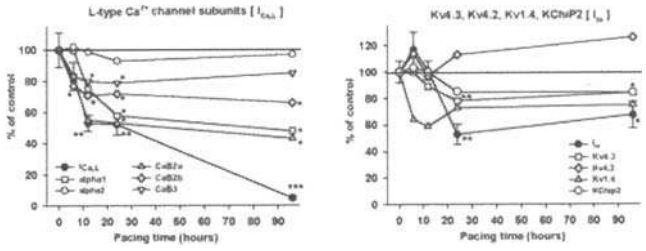
Studies in experimental models have demonstrated that electrical remodeling in chronic rapid atrial pacing reduces L-type Ca^{2+} currents (ICa,L) and transient outward K^+ currents (Ito) by transcriptional downregulation of the underlying ionic channels. Similar observations were made in patients with chronic atrial fibrillation. However, electrical remodeling starts early after the onset of rapid atrial rates. We have previously shown that ICa,L and Ito are decreased within the first hours after the onset of rapid atrial rates. In this study, we present the molecular mechanisms underlying early current changes.

Methods: Rapid (600ppm) right atrial pacing was performed via a transvenously implanted right atrial lead in female New Zealand rabbits. The animals were divided into 5 groups (sham(P0), 6h(P6), 12h(P12), 24h(P24), and 96h(P96) pacing, n=5 for each. mRNA measurements of L-type Ca^{2+} channel alpha1,alpha2delta, CaB2a,CaB2b, CaB2c and of Kv4.3, Kv4.2, Kv1.4 and KChiP2 mRNA were done by one step RT-PCR in right atrial specimen.

Results: The reduction in ICa,L was paralleled by a downregulation of mRNA expression of the alpha1 subunit of the L-type Ca^{2+} channel and of the auxillary subunits CaB2a, CaB2b and CaB3, respectively. alpha2delta mRNA expression was unchanged. Ito changes were also paralleled by a decrease in Kv4.3 mRNA expression. KChiP2 expression was only mildly reduced at 24 and 96h. Kv4.2 and Kv1.4 mRNAs were not affected by rapid atrial pacing.



Rapid ion channel remodeling.

Conclusions: The early changes of ICa,L and of Ito are paralleled by a reduced mRNA expression of the underlying channel alpha and beta-subunits. The mechanism of reduced currents appears to be a transcriptional downregulation of underlying ion channels even in early stages of electrical remodeling.

PULMONARY VEIN ABLATION IN ATRIAL FIBRILLATION

P2757 Collateral damage from circumferential laser energy ablation of pulmonary veins

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Background: Laser energy applied circumferentially at the pulmonary vein ostium is an effective technique for isolation of pulmonary vein from the left atrium. However, the collateral damage profile is unclear.

Method: To determine the collateral damages associated with circumferential laser energy application at the pulmonary vein ostium, 24 pulmonary veins were ablated in 9 dogs. Laser energy was delivered at 3.5 watt/cm to 5.4 watt/cm (average= 4.3) for 120 to 600 seconds (average= 225 seconds). Pulmonary vein and neighboring tissue were examined for acute lung burns, collateral vascular burns, and other tissue injury.

Results: Lung burns were noted in 4 (17%) of 24 pulmonary vein ablation: 8 energy deliveries at left superior pulmonary vein resulted in no left upper lobe lung burn. 6 energy deliveries at left inferior pulmonary vein resulted in 1 left lower lobe hilar lung burn. 9 deliveries at right superior pulmonary vein resulted in 3 right upper lobe hilar lung burns, and 1 delivery at right inferior pulmonary vein resulted in 1 right lower lobe hilar lung burn. No evidence of pulmonary artery, aorta, pericardial, or superior vena cava injury was seen.

Conclusion: Minimal collateral damages were observed with laser energy application at the pulmonary vein ostium. This may support the safety profile for the use of circumferential laser energy ablation in pulmonary vein ablation.

P2758 First experience with circumferential pulmonary vein ablation using a laser energy balloon catheter

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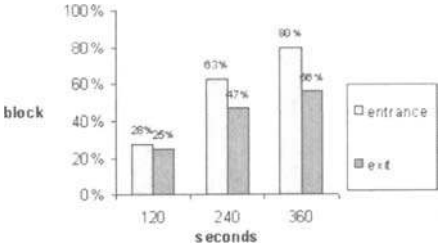
Background: Electrical isolation of pulmonary veins (PV) is crucial to treating atrial fibrillation. Creating bi-directional block of the PV with circumferential lesions at the ostium has been difficult to achieve with radiofrequency energy. Laser energy ablation has been shown to be effective in creating atrial lesions, but the duration of energy application with laser ablation is not clear.

Methods: To determine the time-dependence of laser balloon catheter ablation in creating conduction block at the PV ostium, 32 PVs were ablated in 20 dogs under intracardiac ultrasound and fluoroscopy guidance. 3.1 to 5.4 watts/cm of laser energy were delivered for 120-600 seconds. Efficacy was established acutely as the presence of entrance and exit block in the PV during mapping with a multi-polar catheter positioned across the PV sleeve.

Results: Average laser energy of 4.0 watts/cm at 3.8 ± 2.0 minutes (range from 2 to 10 minutes) was delivered. Entrance block was achieved in 28% (n=9) of lesions after the first energy delivery, in 63% (n=20) after 240 seconds, and 80% (n=26) after 360 seconds. Exit block was achieved in 25% (n=8) of PVs after one energy delivery of 120 seconds, 47% (n=15) after two, and 56% (n=18) after three.



Block time table.

Conclusions: Laser energy is an effective energy source to produce conduction block in PVs. However, energy deliveries of two to three minutes may be required.

P2759 Complications and pulmonary vein anglograms after pulmonary vein ablation

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Pulmonary vein ablation is a new method to treat atrial fibrillation. Therefore its complications in the acute setting are not fully known. We analysed all complications which occurred during the initial hospital stay and one week later after pulmonary vein ablation. In addition we analysed all pulmonary vein angiograms, which were performed before and after ablation of each pulmonary vein. In 76 patients 84 PV-ablations were performed (age 58±8 years). In 174 PVs it was performed either a focal ablation (n=32) or a complete PV-isolation using a circumferential mapping catheter (n=132). Results: In patients with focal PV-ablations we found 7 severe PV-stenosis, and 14 non-severe (<50%) PV-stensosis. In the patient group with PV-isolations one total PV-occlusion occurred, which was dilated successfully during the same procedure. 62% of all ablated PVs showed non-severe stenosis (20-30%). The occurrence of PV-stenosis was dependent on the number of radiofrequency applications (p=0.002) and independent of the PV-localization (p=0.3). 6 patients complained during the following days of severe chest pain lasting from 2 hours to 3 days. None of these patients showed PV-stenosis in the angiograms. One patients suffered from severe singultus, which was refractory to any therapy for weeks. None patient reported about PV-stenosis related symptoms. Conclusion: PV-ablation is correlated with significant morphological changes of the pulmonary vein. Focal ablations within the vein are high risk ablations for severe PV-stenosis. In the majority of the patients PV-isolations led to non-severe PV-stenosis. Hence ostial PV-isolation without ablating within the vein is not feasible in 62% of the patients. Long term effects of such complications might occur in these patients. Therefore a meticulous follow-up is warranted in all patients with PV-ablations in order to detect late PV-stenosis.

P2760 Reasons for relapse of atrial fibrillation after successful pulmonary vein isolation

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Trigger elimination by pulmonary vein (PV) isolation has been proposed to cure drug-refractory atrial fibrillation (AF) with varying success. Reasons for arrhythmia recurrence might include re-conduction or new atrial triggers.

Methods: A total of 158 pts (36 f, mean age 56 ± 10 years) underwent pulmonary vein isolation (125 pts with intermittent AF) for the treatment of atrial fibrillation (mean duration 7.8 ± 6.5 years) after drug-refractoriness to a median of 3 antiarrhythmic medications. After double transseptal puncture, PV isolation was performed in each PV that exhibited a typical spike potential by focal interruption of the conducting myocardial fibres using radiofrequency application (max. 30 W, 50° C over max 180 sec). Loss of the PV spike was demonstrated as endpoint of catheter ablation in each pt at the procedure end.

Results: A mean number of 22.6 ± 10.9 RF applications were used to achieve PV isolation (right upper PV (RUPV) 7.4 ± 5.2, left upper PV (LUPV) 7.9 ± 5.5, left inferior PV (LIPV) 5.7 ± 3.8, right inferior PV(RIPV) 4.8 ± 3.9), which took in mean 306 ± 98 min (42 ± 17.8 min of fluoroscopy). In all pts the LUPV and the RUPV were targeted, in 85% the LIPV and in 42% the RIPV. During follow-up after the initial procedure, 54% (86/158 pts) had a recurrence of AF. A total of 34 of these pts underwent a second ablation procedure. In all pts, re-conduction of at least one previously isolated PV was demonstrated, either inside the PV or by persisting spike potentials at the PV ostium, that were then subsequently ablated (mean number of RF 17.7 ± 9.9, mean duration 303 ± 87,4 min, mean fluoroscopy 38.7 ± 15.9 min.). Subsequently, follow-up resulted in 65% (22/34) of these pts in stable SR.

Conclusion: In all our patients, who previously underwent a successful pulmonary vein isolation procedure, at least one spike potential inside or in close proximity to the pulmonary vein ostium could be demonstrated during the repeat procedure. This underlines the importance of permanent interruption of myocardial fibres and a truly ostial placement of lesions.

P2761 Does the number of disconnected pulmonary veins affect long-term outcome after catheter ablation of atrial fibrillation?

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Backgrounds. The pulmonary veins (PVs) are frequent sources of ectopic beats triggering atrial fibrillation (AF) and therefore electrical disconnection is regarded as the procedure of choice for AF catheter ablation (RFCA). Whether the number of disconnected PVs affects long-term outcome is unknown.

Methods: 70 patients (pts)(57% males, mean age 49 ± 7 years) with idiopathic AF resistant to at least 2 antiarrhythmic drugs (AADs) (including amiodarone and class Ic drugs), were evaluated.56 pts (80%) had paroxysmal AF (pAF)(at least 1 episode/week), and 14 pts (20%) had persistent AF. In all pts PVdisconnection guided by PV angiogram and PV ostium mapping by means of circumferential catheter was performed during sinus rhythm or distal coronary sinus pacing.After procedure pAF pts were discharged without AADs if complete PV disconnection was achieved, or with flecainide if one or more PVs could not be disconnected; amiodarone was maintained in all pts with previuos persistent AF. The furhter follow-up consisted of monthly clinical evaluation and 24 hours Holter recording at 1,3,6 and 12 months (mts).

Results: Complete disconnection of all PVs was achieved in 44 (63%) pts and in a greater proportion of pAF pts (38, 67.9%) than persistent AF pts (6, 42.9%; p: 0.08). One ore more PVs could not be disconnected in 26 pts (37%). Actuarial arrhythmia free cumulative survival was significantly better in pts after disconnection pf all PVs than in those with incomplete disconnection of some PVs (3-, 6-, 12-mts cumulative arrhythmia free survival: 89%, 85%, 75% versus 40%, 35%, 35%; Logrank: $P<0.0001$). Arrhythmia pattern (paroxysmal versus persistent) did not affect long term outcome after complete PV disconnection.

Conclusions: Short and long term outcome is significanly better in pts with complete disconnection of all PVs. In view of this results, complete disconnection of all PVs should be regarded as the endpoint of AF RFCA. Failure to obtain this endpoint should call for a repeat procedure within the same hospitalization

P2762 Comparison of long-term outcome of focal ablation versus pulmonary veins disconnection

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Pulmonary veins (PVs) ostium electrical disconnection have been introduced as an alternative approach to ablation of atrial fibrillation (AF) trigger foci in PVs. Aim of this study was to compare the efficacy of these approaches in preventing AF recurrences.

Methods.110 patients (pts) (61% males, mean age 51±8 years)with lone AF refractory to antiarrhythmic drugs (AADs) were retrospectively evaluated. 93 pts (84.5%)had paroxysmal AF and 17 pts (15.5%) persistent AF.

40 pts (36.4%)underwent focal ablation. Frequent spontaneous ectopies were present during the procedure in 22/40 pts (55%); in the remaining 18 pts without spontaneous ectopies, ablation was perfomed by abolition of the electrogram of the "presumably guilty" PV. Multiple foci were localized in 22/40 pts (55%). Mean number of procedure/pt was 1.8±0.6 (range 1-4)and 36 pts (90%) required at least 2 procedure to prevent AF recurrences.

Electrical disconnection of all PVs was attempted in 70 pts. Complete disconnection of all PVs was achieved in 44 pts (63%), while 1 or more PV were not disconnected in 26 pts (37%). Actuarial arrhythmia free survival analysis revealed better outcome in pts in whom successful disconnection of all PV was achieved (cumulative 3-, 6-, 12 months arrhythmia free survival: 89%, 85%, 75%) than in those that underwent focal ablation either guided by spontaneous ectopies (cumulative 3-, 6-, 12 months arrhythmia free survival: 55%, 52%, 44%)or guided by PV potential abolition (cumulative 3-, 6-, 12 months arrhythmia free survival: 62%, 42%, 20%)(Logrank $p<0.0003$).There was no significant difference in AF recurrence rate among failed PV disconnection pts (cumulative 3-, 6-, 12 months arrhythmia free survival: 40%, 35%, 35%) and PV focal ablation patients.

Conclusions: Due to the frequent presence of multiple foci in more PVs and the inconsistance of spontaneous ectopies in many istances, long term results are significanly better after PV disconnection -provided that all PVs are successfully disconnected- than after focal ablation.

P2763 Electrical pulmonary vein disconnection with multipolar mapping technique: differences of left and right superior pulmonary vein

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Background: Most of the triggers initiating focal AF are located in the left and right superior pulmonary vein (LSPV, RSPV). The extent of ostial ablation necessary to electrically disconnect the pulmonary-vein-left-atrial (PV-LA)- extension, which is limited by the variable anatomy and the risk of PV stenosis, has not been analyzed comparing LSPV and RSPV.

Methods: 20 Pt (age: 55±2 years, 9f) with focal AF, no structural heart disease and an LA < 40mm were included in the study. RF ablation (max. 50°C, 30 Watts) of the arrhythmogenic PVs was performed as proximal as possible, targeting the PV perimeter on the basis of bipoles from a circular mapping catheter (Lasso) showing the earliest activation during SR or pacing from the CS. The ablation catheter was positioned correspondingly on fluoroscopy. Endpoint was the elimination of all PV-LA-extensions.

Results: In the LSPV, PV-spikes were found in 20/20 patients with 1 PV-LA-extension in 12 Pt, 2 in 4 Pt and 3 in 4 Pt. Complete isolation was performed in 18/20 Pt (90%) with 9.6±4.1 RF applications and a cumulative RF duration of 7.2±3.2 min. In the RSPV, PV-spikes were found in 17/20 Pt with 1 PV-LA-extension in 16 Pt and 2 in 1 Pt. Complete isolation was performed in 17/17 Pt (100%) with 5.9±3.7 RF applications ($p<.05$ vs LSPV) and a cumulative RF duration of 5.2±3 min. In 1/20 Pt (5%) a 30% stenosis of both the LSPV and RSPV ostium was found after ablation.

Conclusions: RF ablation for electrical disconnection of the LSPV is more complex compared to the RSPV due to more PV-LA-extensions and needs a significantly higher number RF applications. In this study this did not result in an increase of acute stenosis of the LSPV.

P2764 Long-term follow-up in patients with refractory atrial fibrillation after pulmonary vein ablation using radiofrequency energy

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Pulmonary vein (PV) ablation offers the potential for cure in selected patients (Pts) with paroxysmal atrial fibrillation (AF). However, results of long-term follow up are currently scarce.

Methods: Between 1996 and 1999, 55 patients (mean age 54 ± 10 years, 38 male) underwent radiofrequency energy catheter (max. 50°C, 30-35 W) ablation of PV foci, or ostial isolation of arrhythmogenic PVs. All Pts had refractory and highly symptomatic AF (paroxysmal n = 44, persistent n = 11). 47 Pts underwent a follow up exam with Holter, transesophageal echo-doppler and angio MRI.

Results: 12 of the 47 Pts underwent a focal PV trigger ablation (18 PVs), 37 Pts underwent ostial PV isolation procedure (70 PVs). Mean number of procedures per Pts was 1.6. Early recurrence of AF was noted in 48%. Acute complication: pericardial tamponade in 3, acute PV stenosis in 4. Mean follow up was 24 ± 10 months (range 12-55), 50% of Pts are in sinus rhythm without antiarrhythmic drugs, 31% of Pts are taking antiarrhythmic drugs and experience a clinically important improvement. 19% of Pts are without change in symptoms. 16 of 47 Pts studied in f/u (11 with ostial pulmonary vein isolation procedure) showed a significant pulmonary vein stenosis: 3 pts had a complete occlusion of one PV, 13 pts 18 PV stenosis, of which 3 progressed to complete occlusions. Procedure characteristics (distal or ostial ablation site, No of RF pulses, max. and total power, max. temperature) did not predict PV stenosis. 4 of the 16 patients with a PV stenosis had complained of dyspnea at moderate exertion.

Conclusion: In our patient group, the risk of potential significant pulmonary vein stenosis is 34%, a significant progression of a PV Stenosis to a complete occlusion was noted 3 times. These results need to be considered when recommending pulmonary vein ablation therapy for atrial fibrillation.

P2765 Pulmonary vein stenoses after ostial radiofrequency catheter ablation. Incidence and time course

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Introduction: The segmental radiofrequency catheter ablation (RFCA) for electric isolation of atrial myofibrils crossing into the pulmonary veins (PV) in patients with paroxysmal atrial fibrillation is promising. However, the temporal course of the development of potential PV-stenoses and occlusions is not investigated in consecutive patients undergoing ablation. Methods: Fifty-four patients were treated at 175 PV by RFCA. The minimal PV diameter (DR) was measured ostially and 2 cm post ostially 1 day prior to-, 1 day after- and 3 months after RFCA by magnetic resonance imaging with contrast-enhanced 3D angiography (MRA).

Results: The correlation of diameters of 44 untreated PV by using a standard X-ray angiography resulted in r=0.93 compared to MRA. One day after RFCA, 26/175 PV (15%) had a reduction of DR, 10 of them >30% DR compared to baseline. After 3 months another 12 PV with normal diameters at day 1 showed a DR, and 6 PV with a DR on day 1 demonstrated a progression. Maximum DR observed was 75%. A regression of initial DR was seen in 8 PV - all in PV with an initial DR < 30%. All measured DR of >30% were characterized by a cumulative radiofrequency current delivery at one ostium of > 25000 joules. All patients showing DR were clinically free of symptoms, e.g. pulmonary hypertension.

Conclusion: Observed DR of >30% correlates to the amount of applied radiofrequency energy. Initial DR that disappears after 3 months could be caused by acute edema or intramural bleeding. The results indicate that the induction of a chronic progressive inflammatory process with the development of higher graded PV stenoses and the risk of total occlusion is possible. A long-term non-invasive follow up in this group of patients appears to be imperatively indicated.

P2766 Quality of life in patients with paroxysmal atrial fibrillation after pulmonary vein isolation

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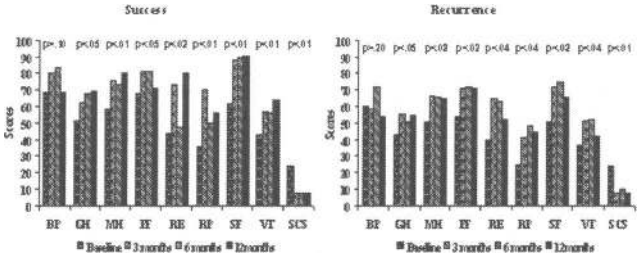
Previous studies have shown that pulmonary vein isolation or segmental ablation (PRFA) in patients with paroxysmal atrial fibrillation (PAF) improved success rate compared to right atrial procedures. However there is no information on quality of life (QoL) after PRFA. The aim of the study was to evaluate QoL of in these patients before and after PRFA.

Fifty six consecutive patients with symptomatic PAF (37 male, mean age: 58 ±10 years) refractory to > 3 antiarrhythmic drugs were enrolled in the prospective study at our institution. The QoL was measured using generic SF-36 scale(BP-Bodily Pain; GH-General Health; MH-Mental Health; PF-Physical functioning; RE-Role-Emotional; RP-Role-Physical; SF-Social Functioning; VT-Vitality) and Symptom Checklist Severity (SCS) scale. The questionnaires were administered before the procedure and during follow- up at 3,6 and 12 months. The scores for patients with clinical success and with PAF recurrence were separately analyzed using ANOVA to discern QoL over time. The differences were considered as significant by error probability $p<.05$.

With the exception of BP scores, all subscales of the SF-36 and SCS were significantly improved after PRFA in 35 pts. without PAF recurrence (see figure, the graphs represent means of scores). In 21 pts. with PAF recurrence an improvement was also found in 7 SF-36 subscales and in SCS. Only in BP scores no significant improvement could be detected.



QoL at baseline and follow-up.

We conclude that PRFA significantly improved QoL in our patients with PAF by reducing arrhythmia related symptoms. Patients with recurrence of PAF also had a benefit in QoL and a significant reduction of SCS although to a lesser extend.

P2767 Analysis of farfield atrial components in left inferior pulmonary vein electrograms

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Pulmonary vein (PV) disconnection requires distinction of extravenous electrogram components from pulmonary venous myocardial potentials. Farfield extravenous components recorded in the left inferior PV (LIPV) have not been studied though their recognition is essential to avoid unnecessary ablation.

Methods: 20 patients (19M, 53±12yrs) undergoing catheter ablation for AF were studied. LIPV recordings were obtained with a circular decapolar catheter before and after ablation and during sinus rhythm as well as coronary sinus (proximal and distal) and left atrial appendage pacing. Selective LAA angiography was performed in 2 views with the circular catheter in the LIPV. RF ablation was performed at PV ostia guided by earliest circumferential activation to eliminate PV arrhythmias and abolish or dissociate all distal PV potentials.

Results: Single potentials or closely separated double potentials (29±8 ms in 6 patients) were recorded in sinus rhythm while during pacing, double potentials were recorded in 17. The larger, sharper second potential was activated radially from the input into the vein where it fused with the first potential. LAA pacing captured the first potential with a longer activation time (47±22ms vs 21±10ms, $p<0.05$) compared to distal CS pacing. Distal and proximal CS pacing did not differ significantly (27±11 vs 21±10 ms). Larger amplitude and sharper activation of the anterior LA below the LAA or close to the bottom of the LIPV ostium coincided with the first potential. Stimulation from this site made the first potential disappear by incorporating it within the artifact. No atrial activation was found coinciding with the second potential which was selectively eliminated by ablation. Angiography showed that the LAA was more than 15mm away from the LIPV in both views in 19/20, as a result, the low LA below the LAA was closest to the electrodes of the decapolar catheter.

Conclusions: Electrical activity originating from the low LA below the LAA and surrounding the ostium can be recorded in 92% of LIPVs. PV potentials can be reliably distinguished by pacing manoeuvers.

P2768 Atrial electrogram components recorded in the right superior pulmonary vein

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Pulmonary vein (PV) isolation is probably the most effective curative treatment for paroxysmal atrial fibrillation. Successful catheter ablation is dependent on recognising venous myocardial components within complex electrograms which include both right and left atrial contributions.
Methods: 20 patients (12M, 30±13yrs) without structural heart disease undergoing catheter ablation were studied. Right superior PV (RSPV), superior vena cava (SVC), complete left and limited right atrial (LA, RA) 3-D activation mapping (Biosense) was performed during sinus rhythm and right atrial pacing, and local activation assigned to the maximum negative dv/dt of simultaneous bipolar and unipolar electrograms.
Results: In sinus rhythm, both the RSPV and SVC were activated from proximal to distal. Double or triple component electrograms were recorded from the anterior RSPV in 18/20 patients, with their separation increasing distally within the PV (from 12±5 proximally to 51±23ms). The initial component of double or triple component electrograms coincided with the surface ECG P wave onset and preceded earliest left atrial septal activation. Its origin was confirmed by recording higher amplitude and sharper electrograms with identical timing from the adjacent SVC. Later sharper components coincided with activation of the high interatrial septum, with progressive delay distally within the vein accentuated by local slow conduction (CV <0.5m/s) observed in 13 patients inside or at the PV os. No significant change was observed in the configuration of complex RSPV potentials during pacing from the low lateral right atrium.
Conclusion: Sequential activation of the SVC, high septal LA, and the RSPV combine to produce complex multicomponent electrograms in the RSPV The initial component represents far field SVC activation, while later components represent activation at the RSPV - LA junction and within the RSPV. Low RA pacing does not change RSPV activation significantly.

P2769 Voltage atrial map analysis to predict atrial fibrillation recurrence in patients undergoing circumferential pulmonary vein ablation

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Background: The safety and efficacy of circumferential radiofrequency (RF) ablation around pulmonary vein (PV) ostia to treat atrial fibrillation (AF) has recently been demonstrated. Identifying factors affecting its success could give insight into the mechanism and aid patient selection. Methods: Between June 1999 and July 2001, 648 patients with resistant paroxysmal (n=419) or permanent (n=229) AF (79% M, age 59±9 years, AF duration 7±2.5 years; 59% with structural heart disease) underwent circumferential PV ablation using CARTO. Patients were followed-up with serial visits, Holter recordings, transthoracic and transesophageal echocardiography. Results: After 18±6 months, 356 patients with paroxysmal AF (85%) and 172 with permanent AF (75%) were AF-free without antiarrhythmic drugs. Among clinical, procedural, echocardiographic and electrophysiological variables examined, significant univariate predictors associated with AF recurrence comprised either pre-RF variables (ie, age>65, left atrial diameter >45mm and bipolar signal amplitude around PV ostia <0.5mV) or post-RF ones (ie, low-voltage [<0.1mV] PV encircled area <15% of left atrial map surface). By multivariate analysis, independent predictors of a higher likelihood of sinus rhythm restoration were post-RF amount of low-voltage encircled area (odds ratio [OR] adjusted for other variables in model, 3.08; 95% confidence interval [CI], 1.66 to 5.72) and pre-RF low-amplitude electrical activity surrounding PV ostia (adjusted OR, 2.86; 95%CI, 1.92 to 4.27). Conclusion: Quantitative voltage map analysis is useful to stratify the risk of AF recurrence after circumferential PV ablation. Measurement of PV ostial electrograms amplitude provides incremental information, as a low "electrical power" in this region appears to identify individuals at risk of recurrence before ablation is performed. These results are clinically relevant as they should be considered in selecting patients for ablation and planning post-procedural management.

P2770 Atrial electroanatomic remodelling time course after circumferential pulmonary vein ablation for atrial fibrillation: is it related to recurrence?

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Background: Circumferential radiofrequency (RF) ablation of pulmonary vein (PV) ostia has evolved as a potential curative therapy for atrial fibrillation (AF). However, few follow-up data are available on left atrial (LA) electroanatomical remodeling induced by this technique. This prospective study investigated the relation between AF recurrence and serial LA electroanatomical changes after ablation, using LA voltage map analysis (VMA) and transthoracic echocardiography (TTE). Methods: 135 consecutive pts with resistant paroxysmal (n=81) or permanent (n=54) AF (67% M; age 60±19 yrs; AF duration 6±2 yrs; 49% with structural heart disease) underwent circumferential PV ablation guided by CARTO. Pts were followed-up with serial visits and Holter recordings. LA VMA and TTE were performed at 3, 6, and 12 months. Results: After 13±2 months, 108 pts (80%) were AF-free without antiarrhythmics. Pts with and without recurrence did not differ in age, AF duration, prevalence of heart disease, and proportion of PVs with complete lesions (bipolar voltage <0.1mV inside the encircled area). Pts without recurrence showed a larger early post-RF low-voltage area, in % of total LA map surface (31±11% vs 21±9%, P<0.001), predominantly due to a greater extent of low-amplitude (<0.1mV) area outside the lesions (P<0.01). During follow-up, in all pts without recurrence the extent of low-voltage area either inside or outside the lesions didn't vary whereas a significant LA size reduction and improvement in its transport function was detected. In contrast, pts with recurrent AF showed a significant and progressive decrease in the extent of low-voltage area involving only the region outside the lesion with not significant changes in LA size and contraction versus pre-RF. Conclusion: Ablation, when effective, results in a profound LA electroanatomical remodeling involving, to some extent, the LA posterior wall to the point that the substrate for AF is no longer present. The phenomenon of voltage amplitude recovery outside the circular line appears to be a key factor for recurrence. Why and how it occurs remains to be clarified.

P2771 Pulmonary vein fibrillation and dissociated activity inside disconnected pulmonary veins

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Paroxysmal atrial fibrillation (PAF) is predominantly triggered by focal ectopies located within the pulmonary veins (PV). Although isolation of arrhythmogenic PV has been introduced as a curative treatment the exact underlying mechanism of PAF initiation has not been completely elucidated. The present study sought to investigate the electrophysiological properties of isolated PV following successful radiofrequency (RFC) catheter ablation.
Methods: Thirty consecutive patients (55±9 years) with recurrent PAF refractory to antiarrhythmic drug treatment were prospectively included. RFC ablation supported by the electroanatomical mapping CARTO (n=21) or conventional approach (n=9) targeted a total number of 52 PV. RFC was applied at the ostial region (max. power 30 W, 50°C). Complete abolition of specific PV potentials were considered as successful ablation. Following functional isolation (FI) the incidence of dissociated pulmonary vein activity and its response to Orciprenalin (Orc, 5mg in 500 ml NaCl) was analyzed.
Results: PV conduction was abolished with a mean of 10.6±6.4 RFC applications in 49 out of 52 potentially arrhythmogenic PVs (94%). After ablation slow dissociated autonomic activity with a baseline rate of 20±7/min was found in 6 PVs of 6 patients (RSPV:n=2, LSPV:n=1, LIPV:n=1, common left PV:n=2). PV-activity increased to 26±9/min during infusion of Orc. After FI sustained or non sustained local fibrillation was recorded within two common left sided PV with preceding autonomic activity. In one patient PV fibrillation occurred during Orc-infusion following a repetetive response to a dissociated automatic rhythm with increasing destabilization and duration. The second patient showed PV fibrillation immediately after the occurrence of PV automaticity. After successful ablation PV-pacing showed no evidence for local capture in all but both patients with common PV and local PV fibrillation.
Conclusions: Slow dissociated automatic rhythms within disconnected pulmonary veins are a phenomenon occurring in about 12% of isolated PV. The unique anatomic substrate of common left PVs seems to predispose to the occurrence of local fibrillation. The initiation pattern of fibrillation within isolated PV demonstrates a possible contribution of multiple factors to the onset and sustenance of PAF.

P2772 Surface electrocardiogram-based T-wave subtraction combined with PV pacemapping for the prediction of pulmonary vein ectopy source

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Background: The surface ECG P wave morphology of ectopics initiating atrial fibrillation (AF) could allow localization and facilitate mapping and ablation of paroxysmal AF. However, because of their coupling interval, most ectopics are concealed by the T-wave and analysis of the P wave morphology is difficult.
Methods: T wave subtraction was performed to unmask ectopic P-wave morphology buried in the T-wave in patients with AF initiation during EP study. The pulmonary vein (PV) source was predicted based on a previously proposed algorithm using the subtracted P wave. PV pacemapping was also performed to compare with subtracted P-waves in order to improve prediction accuracy. The origin of ectopic foci was confirmed by intracardiac mapping and elimination by specific PV disconnection.
Results: Thirty-eight ectopic P-wave morphologies in 34 PAF patients with ectopics or mappable AF initiations were prospectively analyzed. Four foci originating from atrial foci were excluded. Correct prediction of PV ectopy origin was achieved using the P-wave algorithm alone in 28/34 ectopics (82%, 11/11 in RSPV, 12/18 in LSPV, 2/2 in LIPV and 3/3 in RIPV). In 6 patients, ectopics from the LSPV were erroneously ascribed to the RSPV (n=3) because of an unusually high amplitude positive P-wave in lead I; or to the LIPV (n=3) because of an unusually low amplitude P-wave in lead II and III. PV pacemapping with 11-12/12 leads match increased correct prediction to 32/34 (94%).
Conclusions: Accurate unmasking of the ectopic P-wave morphology concealed within the preceding T-wave in conjunction with pacemapping from the PVs allows quick and accurate localization of 94% of PV ectopic foci to facilitate rapid targeting of arrhythmogenic PV. This technique may also allow non-invasive recognition of multiple ectopics from different sources.

P2773 Intraoperative evaluation of bilateral pulmonary veins isolation: unipolar versus bipolar radiofrequency energy application

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Eight patients (pts) (2 female, 58±12 yrs) with paroxysmal atrial fibrillation (AF) (duration 39±20 months) were submitted to AF surgery, concomitant with myocardial revascularization in 2 pts and myomectomy in 1 (HOCM). AF was idiopathic in the remaining 5 pts. AF surgery consisted of bilateral isolation of pulmonary veins (PV) using radiofrequency (RF) energy applied epicardially by a heptapolar catheter (Thermaline) - 5 pts - or a novel system (AtriCure) - 3 pts. For the first, each set of <= 7 simultaneous applications aimed at a maximal duration of 2+2 min, preset temperature <= 80°C and output <= 150 Watts. With the novel system, we performed bipolar applications; energy delivery was controlled by impedance monitoring and applications were ended after abrupt, sustained elevation of impedance (peak temperature achieved was 49 ± 7 °C and applications took 8.3 ± 3.1 sec). Epicardial bipolar voltage mapping (CARTO) was performed before and after the RF procedure. Using the navigator catheter, points were recorded at the insertion of each PV and at the non-isolated left atrial posterior wall (average 10 points/map). The amplitude of the local electrograms (LE) was measured before and after RF applications. If LE amplitude inside the isolated zone was not < 0.1 mV and not reduced by >80%, a second application was performed. A maximum of 2 epicardial applications was allowed in each pt and if the final result was unsatisfactory, further endocardial applications were performed.
Results: Baseline LE amplitudes were invariably > 1.0 mV. Successful isolation of right PV was achieved in 7 pts: after 1 set of applications in 5 pts (2 treated with AtriCure) and a second set in 2. Left PV isolation required 2 sets of epicardial applications in all pts, being successful in only 2 (both treated with AtriCure); 4 pts received endocardial applications, successful in 3. Overall, bilateral PV isolation was achieved in 5 pts.
Conclusions: CARTO bipolar voltage mapping is a fast, simple means for evaluation of PV isolation. Epicardial PV isolation is achieved easier in the right PV. Bipolar RF isolation is a faster procedure than conventional unipolar ablation and seems to be at least as effective.

P2774 Temporal course of relapses after radiofrequency catheter ablation of the pulmonary vein ostia in patients with paroxysmal atrial fibrillation

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Introduction: Focal radiofrequency catheter ablation (RFCA) of the trigger substrates in the pulmonary veins (PV) or complete isolation of the ostia cannot modify the substrate in a way that prevents atrial fibrillation (AF) in the atria as the MAZE-III-surgery. We tested the hypothesis whether early relapses may be counteracted by inverse electric remodelling due to a reduction of AF burden. In such a case a long term success of RFCA, although early relapses are observed, could be possible.
Methods: In 48 patients (mean age 51±10years, male=31) with frequent drug-refractory episodes of AF (> 10/month) an 48-hours Holter ECG (HECG) was performed 24 hours after RFCA of atrial fibrillation. Twenty-six patients had lone atrial fibrillation and 22 patients had a mild heart disease, including hypertensive cardiomyopathy and CAD with normal ejection fraction and normal atrial dimensions. During the follow-up (FU) all patients received at discharge and x = 5.9 months ordinary two eventrecordings (ER) with evaluated automatic arrhythmia detection for 3 weeks each.
Results: At HECG after ablation, 20/43 (47%) patients showed relapses of AF. AF-relapses occurred in 21/43 (49%) patients during ER. Fourteen (33%) patients had early and late relapses observed during the HECG and ER after ablation. However, 6/43 (14%) patients showed AF relapses during the initial HECG, proved to be free of relapses in the FU. 51% of the patients did not show any documented AF during the whole FU. Antiarrhythmic drugs were continued in 4 patients with observation of AF-relapses at HECG and in 5 patients with observation of sinus rhythm. The antiarrhythmic drugs were continued in 7 patients with observation of AF during ER and in 4 patients with sinus rhythm.
Discussion: Comparable with the results after Mini-MAZE-surgery (reduced number of lessions compared to MAZE III) 14% of our observed patients showed early relapses without further ones. This observation can be explained with the hypothesis given above.

P2775 Analysis of P-wave morphology during pulmonary vein ectopic activity

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Background Ablation of focal activity, most commonly from the pulmonary veins, can reduce the occurrence of atrial fibrillation (AF). Because of the infrequent, unpredictable nature of this focal activity, algorithms have been derived to allow prediction of the arrhythmogenic pulmonary veins, by analyzing the P wave morphology from a standard 12 lead ECG. This report investigates P wave morphology during pulmonary vein ectopic activity in patients with AF and in normal controls.
Methods The study enrolled 55 patients, 40 consecutive patients with symptomatic, drug refractory AF scheduled for focal ablation and 15 controls undergoing ablation of supra-ventricular tachycardia. AF patients were subdivided into those with paroxysmal or persistent AF at the time of the study; and those with electrically and structurally 'normal' (defined as maximum LA size < 4.5 cm, total P wave duration < 100 msec and P wave dispersion < 60 msec.) or 'abnormal' atria.
P wave morphology on 12 lead ECG was analyzed during spontaneous ectopy and published algorithms were used to predict the culprit PV. Further analysis of P wave morphology was undertaken during decremental cycle length pacing from the PVs.
Results The various algorithms designed to predict the PV generating ectopic activity have similar predictive accuracy. Accuracy is highest in patients with paroxysmal AF and normal atria (93%), but much less in patients with abnormal atria (64%) or persistent AF (51%).
P wave morphology during pacing from the pulmonary veins is similar to spontaneous ectopy, if performed at similar coupling intervals. P wave morphology can vary with cycle length. In patients with abnormal atria or persistent AF, a significant change in P wave morphology was observed in 25% as cycle length shortened.
Conclusion P wave morphology during ectopic activity from the pulmonary veins is affected by cycle length and the presence of underlying atrial electrical and structural abnormalities. This reduces the accuracy of non invasive methods in localizing arrhythmogenic veins.

P2776 Early recurrences of atrial fibrillation are not predictive for the long-term success of pulmonary vein ablations

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The recurrence rate of atrial fibrillation after pulmonary vein ablation ranges from 30% to 50%. The significance of early or late recurrences of AF are unknown. Therefore we did a close detailled follow-up of all patients who were treated by PV-ablations. All patients received Holter-Monitorings and event-recorder immediately after the ablation procedure. All antiarrhythmic drugs had to be discontinued and were not initiated if the patient had AF recurrences during the first month after PV-ablation. Results: 52 patients (52±9 years) were followed up 10±5 months after PV-ablation. 19 patients were free of any AF recurrences during this period. In 34 patients one AF recurrence was at least detected. In 8 patients of this group a early AF recurrence was found (14±12 hours after PV-ablation). The remaining first recurrences occurred 28±20 days after the procedure. While 6 patients with early AF recurrences did not report any further recurrences during the following 5±6 months, all patients with late recurrences did report further AF episodes. Cardiac disease, atrial diameters or characteristics of AF were not predictive für early recurrences ($p>0.05$). Conclusion: Early AF recurrences did not mean failure of the PV-ablation, because these episodes were not predictive for the long-term success of the ablation. Prophylactic antiarrhythmic therapy after early AF recurrences are not justified. A second early intervention does not seem appropriate.

P2777 The significance of early atrial fibrillation recurrence post pulmonary veins isolation

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Background: The majority of atrial fibrillation recurrences post pulmonary veins (PV) isolation occurs within the first 4 weeks. The significance of this early recurrence of AF remains unclear. We compare long-term follow-up in patients with early versus late recurrence of AF post PVs isolation.
Methods and Results: Two hundred and forty patients underwent circular mapping guided PVs isolation (190men; mean age 54±11 years) for treatment of symptomatic AF. All patients underwent ostial isolation of all PVs. Eighty-nine patients (37%) experienced recurrence of AF within the first 2 weeks post PVs isolation. All patients with recurrence of AF underwent pharmacological or DC cardioversion and were started on a limited 6 weeks antiarrhythmic drug (AAD) trail. After a mean follow-up of 8±4 months 62% (56/89) remained in SR (group 1), and 37% (33/89) continued to have AF > 6 weeks post PVs isolation. The table shows demographics and follow-up results of the 2 groups.

	Group 1	Group 2	P value
Patients	56	33	ns
Age (years)	53 ± 8	55 ± 9	ns
Ejection fraction %	52 ± 8	51 ± 9	ns
Left atrial size (cm)	4.1±0.3	4.3±0.5	ns
Duration of AF	6.1 ± 3.4	6.4 ± 3.5	ns
Follow-up (months)	8±3	7.5 ± 3	ns
In AF after AAD	none	100% (33/33)	p<0.05
2nd ablation	none	42% (14/33)	p<0.05
Chronic cure (no AAD)	100%	42% (14/33)	p<0.05
Chronic cure (on AAD)	none	51% (17/33)	p<0.05

AAD=antiarrhythmic drugs

Conclusion: Early recurrence of AF post circular mapping guided isolation of all PVs does not seem to reflect true procedural failure. From our preliminary data short term AAD trail prior to 2nd ablation procedure seems to be an appropriate approach in this group of patients.

P2778 Is complete pulmonary veins isolation necessary to reduce the recurrence rate after RF ablation of atrial fibrillation?

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Localizing and ablating the focal triggers of atrial fibrillation (AF) has been proven an effective approach for radiofrequency (RF) AF ablation, but this strategy is time consuming and often requires multiple procedures. So, empirical electrical isolation of all pulmonary veins has been suggested as the best method to treat these patients. The purpose of this study was to assess the relationship between the number of pulmonary veins empirically isolated during the first RF ablation for paroxysmal AF and recurrence.
Patients and Methods: The study included 35 consecutive patients (24 male; mean age 51 years old) who had frequent symptomatic paroxysmal AF refractory to at least three antiarrhythmic drugs. Using the lasso decapolar catheter (J&J) for mapping and a 4-mm distal tip catheter, two to four pulmonary veins were ablated at the venoatrial junction (30 W and 500 C), aiming to achieve electrical isolation of the veins. The patients were periodically followed with loop recorder monitoring.
Results: Ninety-three veins were ablated (LSPV: 34; RSPV: 31; RIPV: 16; LIPV: 12). True electrical isolation could be achieved only in 61(65%) veins (LSPV: 68%; RSPV: 71%; RIPV: 50%; LIPV: 67%). After ablation 23 (66%) of 35 patients presented recurrence (< 48 h: 12; < 30 days: 10; > 30 days: 1). Six patients had not any vein isolated, all presented recurrence; 18 patients had one or two veins isolated, 15 (83%) presented recurrence and 11 patients had three or four veins isolated, 4 (36%) presented recurrence ($p < 0,05$).
Conclusion: Empirical isolation of pulmonary veins appears to be an effective approach to avoid recurrences in patients with paroxysmal AF when three or four true electrical isolations are achieved.

BIVENTRICULAR PACING AND HEART FAILURE

P2779 Biventricular pacing has both arrhythmogenic and antiarrhythmic effects: results from the MUSTIC study

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Atrial and ventricular arrhythmias are frequent in patients with severe heart failure due to chronic left ventricular systolic dysfunction and may influence prognosis. The aim of this study was to assess the incidence of arrhythmias and the influence of biventricular pacing in the MUSTIC study patients.
The MUSTIC study was a randomized, crossover, single blinded study including patients with chronic severe heart failure,stable sinus rhythm, and intra ventricular conduction delay (QRS > 150ms). Patients were implanted with a DDD BiV pacemaker and entered a 6-month crossover phase with the pacemaker programmed active (BiV) or inactive (VVI 40 bpm) during 2 periods of 3 months each. At the end of the crossover phase the pacemaker was programmed BiV and patients were re-assessed 6 months (FU) later. 24-hours ECG recording was performed at baseline, randomisation time (Rando), at the end of each 3-month crossover period, and at FU. 28 patients had complete data. The median number of premature atrial contractions (PAC), premature ventricular contractions (PVC), ventricular tachycardia (VT) and atrial fibrillation (AF) episodes are summarized in the table.
Results:

	Baseline	Active	Inactive	FU
PAC	26.5	17	88.5	47
PVC	122.5	158.5*	301**	57
VT	0	0	1	0
AF	0	1	0	0

* p<0.05 vs baseline, ** p<0.05 vs active

Conclusion: Implanting a biventricular pacing system is associated with a significant increase in the incidence of PVC's, and at a lesser degree of PAC's. This "arrhythmogenic" effect could be of mechanical origin (intracardiac leads). However it was principally observed with the device programmed inactive, and decreased over time during active biventricular pacing.

P2780 Resynchronisation therapy in patients with and without sinus rhythm

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Resynchronisation therapy (RT) in patients (pts) with severe heart failure (CHF) and left bundle branch block (LBBB) improves clinical symptoms and myocardial function. However, conflicting data exist for pts. with atrial fibrillation (AF) or preexisting DDD-pacemaker (PM).
We analysed 196 pts. (mean age 61 years (y), 109 with DCM, 71 with CAD, 17 with other underlying diseases, mean FU 12 ± 9 m) who received RT with respect to the underlying rhythm at baseline. Analysis of baseline characteristics in the different groups shows no statistical differences between the SR-pts. and the non-SR-pts. (11xAF, 4xVVI-SM, 8x intermittent AF, 15x DDD-PM) concerning age, NYHA class, peak oxygen consumption (VO2peak), oxygen consumption at anaerobic threshold (VO2AT), workload, 6-min walking distance, LVedD, LVEF). QRS is wider due to PM stimulation in the non-SR group (199 ms versus 186 ms) and the proportion of pts. with valvular disease is larger (15.7% versus 5.1% in SR). After 3, 6 and 9 m however, the clinical course in the non-SR group seems less favorable (table), suggesting a more advanced disease in these pts. The number of Subanalyses for pts. with chronic AF, intermittent AF, any AF and DDD-PM show, that the main cause for deterioration is any kind of AF at baseline.

	SR			NonSR		
	pre (n=158)	6 m (n=111)	9 m (n=90)	pre (n=38)	6m (n=27)	9 m (n=23)
NYHA	3.1±0.3	2.2±0.5*	2.3±0.6*	3.1±0.3	2.5±0.8*#	2.4±0.7*
VO2peak	13.0±2.9	15.1±3.3*	16.0±4.2*	11.8±1.9	12.6±5.3#	12.2±2.3#
VO2AT	10.8±2.5	12.6±3.9*	13.1±3.1*	10.3±1.7	12.1±5.4	9.6±1.0#
LVedD (mm)	82±11	73.8±13.8*	75.3±12.5*	78.0±10.4	73.8±12.4	73.6±15.8

Our data show a favourable outcome after RT for pts. with normal SR. However in pts. with preexisting AF or AV-block III with DDD-PM the clinical benefit seems to be less sustained. These results are comparable to those of the AF-arm in MUSTIC.

P2781 Continuous improvement in heart rate variability with biventricular pacing in patients with severe heart failure: the MUSTIC study

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Heart rate variability (HRV) is frequently impaired in patients with severe heart failure and is an independent prognosis factor. The aim of this study was to assess the effects of biventricular pacing (BiV) in a subgroup of the MUSTIC study patients. This randomized, crossover, single blinded study included patients with chronic severe heart failure, intra ventricular conduction delay (QRS > 150ms) and stable sinus rhythm. Patients were implanted with a DDD BiV pacemaker and entered a 6-months crossover phase with the pacemaker programmed active (BiV) or inactive (VVI 40 bpm) during 2 periods of 3 months each. After the crossover period the pace maker was programmed on a BiV mode and patients were followed for 24 months more. 24-hours Holter recording was performed at baseline, randomization time (rando), at the end of each crossover period and then after 3 (FU I) and 6 months (FU II). Patients who didn't complete the 2 crossover periods (n=18), or with > 20% atrial paced cycles (n=5) or poor data (n=3), were excluded from the analysis. No modification in drug treatment was allowed from the time of inclusion until the end of the crossover phase. Heart rate variability analysis (time domain measurements) was performed in the 22 eligible patients. Main results are summarized in the table.

	Baseline	Rando	Active	Inactive	FU I	FU II
pNN50 (%)	5.2±5	3±3	15.3±9	9±8*	17±9**	13±8**
RMSSD (ms)	27±11	23±7	41±12	38±22	49±14**	48±24**
ASDNN (ms)	35±10	33±10	40±9	36±12	45±8**	39±16**
SD (ms)	85±31	87±24	98±31	82±16*	94±34	103±46**

* p<0.05 vs BiV, ** p<0.05 vs baseline

Conclusion: HRV was significantly higher with biventricular pacing as compared to no pacing during the crossover phase. Improvement of HRV with biventricular pacing was preserved over time until at least one year.

P2782 Spontaneous conversion of chronic atrial fibrillation as potential benefit of biventricular pacing in patients with congestive heart failure

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Atrial fibrillation (AF) is a common problem in patients (pts) with congestive heart failure (CHF). It has been shown in former studies that biventricular pacing may lead to hemodynamic improvement in selected pts with CHF. The impact of chronic biventricular pacing on recurrence and stabilization of sinus rhythm (SR) in pts with CHF and permanent AF remains unclear.
Patients/ Method: In 14 pts with CHF NYHA class III-IV (6 pts with chronic refractory AF, 8 pts with SR) biventricular devices (Pacesetter Frontier™ 5200, St. Jude Medical; Contak TR™ or Contak CD™ CHFD™, Guidant) were implanted. Electrocardiogram (ECG), Holter-ECG and echocardiography were performed before implantation and during follow up (time between 2 and 19 months). Left ventricular ejection fraction (LVEF), left atrial diameter (LAD), left ventricular enddiastolic diameter (LVEDD) and mitral valve insufficiency (MI) were used as parameters for hemodynamic assessment.
Results: All pts showed an improvement of LVEF, NYHA class, LAD and LVEDD. In 67% of pts with chronic refractory AF at time of implantation spontaneous conversion into SR occurred 1, 3, 10 and 19 months after implantation due to a significant (p<0.05) improvement of LVEF, reduction of LAD/LVEDD and a decrease of MI (table), 33% of pts. remaining in AF showed no significant improvement in hemodynamics.

Hemodynamic parameters

N=4	AF	SR
LVEF (%)	17 ± 5 (p<0.05)	37 ± 11 (p<0.05)
LAD (mm)	53 ± 7	46 ± 7
LVEDD (mm)	68 ± 6	63 ± 8
MI	II-III	I-II

AF: atrial fibrillation; SR: sinus rhythm; LVEF: left ventricular ejection fraction; LAD: left atrial diameter; LVEDD: left ventricular enddiastolic diameter; MI: mitral valve insufficiency

Conclusion: The potential benefit of biventricular pacing due to hemodynamic improvement may result in obtaining sinus rhythm in pts with CHF and chronic AF. Further studies are necessary to answer the question, if the prophylactic implantation of an atrial lead during AF is useful.

P2783 Resynchronization therapy significantly reduces mitral regurgitation in congestive heart failure patients

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Mitral regurgitation (MR) plays an important role in the pathophysiology of congestive heart failure (CHF). Its contribution in long term prognosis, however, is still unclear. Biventricular pacing (BiV) improves clinical status and functional class in CHF patients, but the underlying mechanisms are not completely understood. We analyzed the beneficial effects of resynchronization therapy in term of reduction of MR. 33 pts (25 man, 72±6 y.o.) with cardiomyopathy of any etiology underwent BiV implantation in our institution. All pts were in NYHA class III/IV despite optimal medical treatment, with a mean ejection fraction (EF) of 23±5% and a QRS duration of 196±25 ms. In all pts v-wave was invasively measured with Swan-Ganz catheter at baseline and after 15 min of BiV. Before and one week after implantation all the subjects underwent complete echocardiography examination in order to determine EF, systolic mitral annulus diameter (SMAD), mitral regurgitation area (MR area), MR area percentage of left atrium area (%MR area), mitral regurgitation score (MR score). Pre and post BiV data are summarized in the following table.

Data pre and post BiV

	PRE	POST	p
EF %	23,24 ± 5,43	33,39 ± 6,91	<.001
SMAD (mm)	39,69 ± 3.06	36,25 ± 4,37	<.001
MR area (cm^2)	7,47 ± 4,9	4,4 ± 3,81	<.001
% MR area	24,54 ± 13,76	5,62 ± 13	<.001
MR score (1-4)	2,14 ± 0,83	1,47 ± 0,59	<.001
v-wave (mmHg)	26 ± 11	17,4 ± 9,7	<.05

These observations confirm the important role of MR in the pathophysiology of CHF and suggest that the beneficial effects of resynchronization therapy may also be related to the partial correction of MR.

P2784 Cardiac resynchronization therapy in advanced congestive heart failure: mid-term clinical and haemodynamic results

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Background: Cardiac resynchronization therapy (CRT) by biventricular pacing (BIV P) has been recently proposed as a means to improve hemodynamics and symptoms in patients (pts) with advanced congestive heart failure (CHF) and interventricular conduction delay (IVCD).
Objective: The aim of this report was to analyze the mid term clinical and hemodynamic results of CRT.
Methods: Between March 1999 and January 2002, CRT was attempted in 117 pts (age 62±9 years; 98 male; n=63 idiopathic, n=39 ischemic, n=15 valvular etiology) with advanced CHF despite optimal medical therapy and IVCD. At baseline NYHA class was 3.0±0.5, QRS duration 180±34 msec, echo LVEF 25±7%, LVEDV 276±88 ml, LVEDD 71±8 mm, MR grade 2.2±1.1, VO2 max 12.9±3.0 ml/min/Kg. Cardiac index (CI) and wedge pressure measured by right heart catheterization were 1.9±0.4 l/min/m^2 and 15±9 mmHg respectively. 12% of pts were in chronic atrial fibrillation; 16% had a pacemaker already implanted and 7% an implantable cardioverter defibrillator. The mean number of hospitalizations/pt for worsening heart failure in the 12 months before enrollment was 1.2±1.3.
Results: CRT was not feasible in 14 pts (10%). After the implantation, the QRS duration shortened to 156±20 msec. After a mean follow up of 9.6+5.0 months, NYHA class was 2.2±0.5 ($p<0.01$), LVEF 28.7±8.% ($p< 0.01$), LVEDV 231±85 ml ($p< 0.01$), LVEDD 68±9 mm ($p<0.01$), MR grade 1.7±0.9 ($p<0.01$), VO2 max 14.5±3.7 ml/Kg/min ($p< 0.01$), CI 2±0.4 (p: n.s.), wedge pressure 11±7,6 mmHg ($p<0.05$). There were 21 cardiovascular hospitalizations in 13 pts. Seven pts died (6%; 4 refractory CHF, 1 ventricular fibrillation, 1 sudden cardiac death, 1 sepsis complicating the replacement of a dislodged left ventricular lead). Concerning HTx candidates: one pt died while awaiting, 2 pts were excluded from the waiting list because of clinical improvement, 2 pts were succesfully transplanted and 7 pts are alive awaiting for HTx.
Conclusions: Our preliminary experience shows that CRT is feasible in the majority of pts. Symptoms, echocardiographic parameters, exercise capacity and hemodynamics significantly improved after implantation with reduced need for hospitalization. In some pts CRT may prevent or postpone the need for HTx or provide a bridge to HTx. These results need to be validated from ongoing randomized controlled trials.

P2785 Magnitude of systolic improvement with resynchronization therapy predicts magnitude of clinical benefit for heart failure

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Cardiac resynchronization therapy (CRT) with left ventricular (LV) or biventricular pacing has been shown to improve LV systolic function and to increase exercise capacity, quality of life, and functional status of heart failure (HF) patients with intraventricular conduction delay. We analyzed results of the completed PATH-CHF II CRT study to test the hypothesis that the magnitude of hemodynamic improvement with CRT predicts the magnitude of clinical benefit with CRT.
Methods: Patients were randomized to 3 months LV pacing followed by 3 months no-pacing or vice versa. Patients were prospectively stratified into equal groups with QRS between 120-150 msec and QRS greater than 150 msec. Changes in peak VO2 measurements from adjacent no-pacing and pacing periods were available from 71 randomized HF patients (NYHA class II&III, EF<30%). The LV max dP/dt and aortic pulse pressure (PP) with pacing at the programmed device settings were measured acutely from LV and aortic pressure recordings. Comparisons were made by unpaired t-test.
Results: The median hemodynamic change with CRT was 13.8% for max dP/dt and 5.1% for PP. Patients with QRS>150 msec or above-median increase in max dP/dt (but not PP) had significantly larger increase in peak VO2 (table). A max dP/dt increase greater than 5% predicted a positive VO2 change with 75% accuracy and had a 80% positive predictive value and a 63% negative predictive value. QRS had a maximum predictive accuracy of 69%.

Predictor	Peak VO2 Change Predictor > Median	Peak VO2 Change Predictor < Median	P Value
QRS	2.31 ± 2.7	0.32 ± 2.3	0.001
max dP/dt	2.24 ± 2.7	0.35 ± 2.4	0.004
PP	1.78 ± 2.7	0.84 ± 2.7	0.153

Peak VO2 Change (ml/min/kg) with CRT (mean ± SD)

Conclusion: Long QRS with HF is known to predict increased contractile function with CRT. Our results indicate that acute increase in contractile function also predicts improved exercise capacity after three months of treatment. This relationship may explain why patients with longer QRS have larger clinical benefit with CRT.

P2786 Interventricular delay increases stroke volume in cardiac resynchronization patients

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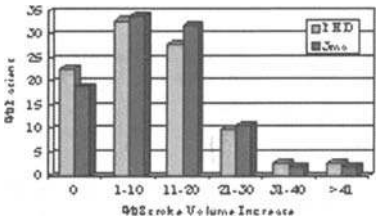
Cardiac resynchronization therapy (CRT) has been demonstrated in prospective, randomized, controlled trials to improve patient functional status and exercise capacity. CRT is currently delivered with simultaneous RV and LV pacing. Enhancement to CRT may be provided by adjusting the relative timing of the RV and LV activation (sequential biventricular pacing). The objective of this study was to compare the optimal sequential biventricular pacing interval to simultaneous biventricular pacing.
Methods: Heart failure patients with dilated cardiomyopathy and interventricular conduction delay were implanted with the InSync III CRT device. Pulsed-wave Doppler echocardiography was used to optimize each supine resting patient's A-V delay by maximizing LV filling, and then V-V timing by maximizing the velocity time integral measure of LV stroke volume at the aortic valve annulus. V-V timing was measured at both baseline and at 3 months at simultaneous (0), 20, 40, and 80 ms with either LV or RV first.
Results: In 300 pts (59% male, age = 66±11 yrs, QRS duration = 164±22 ms) included in this study, stroke volume was optimal at simultaneous biventricular pacing in 23% pts. and at sequential biventricular pacing with LV first in 54% pts. and with RV first in 23% pts. In 16% pts., sequential biventricular pacing provided a greater than 20% incremental improvement in stroke volume. Similar results were observed at 3 months (Figure).



Conclusions: This study demonstrated that in 77% of CRT pts., sequential biventricular pacing consistently provides an improvement in stroke volume compared to simultaneous biventricular pacing. These results suggest that independent pacing ability between the RV and LV provides an incremental hemodynamic benefit during cardiac resynchronization.

P2787 Optimized left ventricular systolic function through asynchronous biventricular pacing

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Biventricular pacing (BiP) can improve left ventricular (LV) function in congestive heart failure (CHF) and left bundle branch block. Acute hemodynamic studies have shown that despite broad QRS isolated LV pacing (LVP) is often superior or equal to BiP. We investigated the impact of asynchronous BiP (asyBiP) on acute LV systolic function.

Methods: 13 pts (3 female, 6 ischemic CHF, 7 non-ischemic CHF), ejection-fraction 24± 8%, NYHA>3) were included. LV hemodynamic response was evaluated by the first derivative of LV pressure (+dP/dt) recorded by a catheter with micromanometer (Millar®). During atriobiventricular-pacing the AV intervall was optimized along the LV pressure curve and kept constant. For asyBiP 8 interventricular delays were tested (20 ms steps, ±80 ms).

Results: To ensure 100% pacing at an intrinsic intervall of 911±242 ms an average intervall of 744±113 ms was necessary. Compared to baseline +dP/dt (801±179 mmHg/s) the maximum hemodynamic response was obtained by asyBiP in 9 pts, BiP or LVP in 3 pts and RVP in 1 pt. In 2 pts neither pacing mode could increase LV+dP/dt. The optimized RV/LV -delay was highly variable ranging from -20 ms (RV stimulated first) to + 80 ms (LV stimulated first). In 8/9 pts with positive response by asyBiP the LV had to be stimulated ahead of the RV.

LV-systolic function and QRS duration

	RVP	LVP	BiP	AsyBiP
dP/dt (mmHtg/s)	865 (±221)	1054 (±261)*	1074 (± 287)*	1126 (±292)**
QRS (ms)	195 (±33)	208 (±37)	151 (±19)*	152 (±24)*

mean values (± standard deviation)*p<0.01 vs. RVP, **p<0.01 vs. BiP and LVP

Discussion: Asynchronous biventricular pacing may compensate differences in excitation propagation due to stimulation site. Synchronized LV contraction may therfore be achieved by asynchronous stimulation. Invasive testing prior to implantation allows resynchronization therapy to be adjusted to individual needs.

P2788 Left ventricular versus biventricular pacing in chronic heart failure: a stress-echocardiographic study

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Acute left ventricular (LV) pacing has been shown to improve hemodynamics in patients with chronic heart failure (CHF) and left bundle branch block to the same extent as biventricular (BI) pacing. However, less information is available on hemodynamic effect of LV pacing during exercise. To address this issue, LV vs BI pacing modes were compared during stress-testing echocardiography.

Methods: Study population consisted of 12 patients with CHF (3 women, age 65.3±8.8 years) due ischemic (n=4) or idiopathic dilated cardiomyopathy (n=7) and/or corrected aortic valve disease (n=1). At baseline, all patients presented with significant left ventricular dysfunction (LVEF 23.8±2.3%) and dilatation (LVEDD 74.4±7.3mm), and intraventricular conduction delay (QRS > 150 ms). They underwent BI pacing system implant (InSync III, Medtronic Inc) that allows separate pacing of the LV, and were evaluated more than 3 months later. Stroke volume (SV) was measured by echocardiography using VTI formula with a sample volume placed in the LV outflow tract (System V, GE-Vingmed) before and during each 3 min period of bicycle exercise with stepwise workload increase of 25 W (Marquette). Both blood pressure and heart rate were measured along with SV. Stress-test was performed in the morning on two consecutive days. Patients were randomly allocated to either BI pacing or to LV pacing mode with a cross-over on the next day.

Hemodynamic changes on exercise

Exercise step	No of pts	SV-BI (l/min)	SV-LV (l/min)	p<
Rest	12	3.01±0.62	3.39±0.57	0.01
25 W	12	4.22±0.89	4.79±1.05	0.01
50 W	11	5.36±1.14	5.64±1.11	n.s.
75 W	8	5.70±1.19	6.50±1.64	n.s.
100 W	3	5,96±0.92	6.73±1.44	n.s.

Results: Exercise tolerance was similar for both pacing modes and all patients terminated test for dyspnea. There were no significant differences in blood pressure during exercise in each pacing mode. Major study results are summarized in the table.

Conclusions: LV pacing results in better hemodynamic response as compared with BI pacing in patients with CHF, both at rest and during dynamic physical exercise. This finding provides support for controlled clinical studies comparing efficacy of LV and BI pacing modes.

P2789 Activation time difference between right and left ventricle – A potential new discrimination algorithm for biventricular ICDs

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Cardiac resynchronization therapy (CRT) by biventricular (BV) pacing improves hemodynamics and functional capacity in patients (pts) with heart failure (HF) and left bundle branch block (LBBB). Many HF pts are at risk of developing sustained ventricular tachyarrhythmias (VT) and are thus in the need for implantable cardioverter-defibrillator (ICD) backup. Inadequate therapies due to supraventricular tachycardia (SVT) are still a limitation in modern ICDs and may be prevented by VT/SVT discrimination algorithms. We investigated whether the activation time difference (ATD) between right (RV) and left (LV) ventricular electrode may be used for VT/SVT discrimination in a BV-ICD. In 16 HF pts (15 males, 63±13 yrs., 7 ischemic, 9 non-ischemic HF, PR 229±63 ms, QRS 176±27 ms, all LBBB) an invasive electrophysiological (EP) study was performed placing EP catheters in the anterior interventricular (AIV), the posterior or lateral (PLV) vein, in the RV apex (RVA), then outflow tract (RVOT) and the high right atrium (HRA). Pacing was performed at cycle lengths (CL) of 500, 400 and 300 ms from proximal and distal AIV/PLV, RVA, RVOT and HRA; ATD between RVA/RVOT and the latest activated PLV site was measured at each pacing site/CL and during induced VT.

Results: 6 VTs were induced in 5 pts (mean CL 325±36 ms). For an ATD difference (Delta-ATD, sinus rhythm (SR) vs. paced/VT) cut-off of 20 ms specificity for VT detection was 100%, sensitivity 86.7% for all pacing sites and RVA or RVOT sensing. For RVA sensing and only LV pacing sensitivity increased to 96.1%, with addition of a V>A criterion to 100%. All induced VTs were correctly classified.

Conclusion: Measurement of RV-LV-ATD may be a new efficient VT/SVT discrimination algorithm for the use in BV-ICDs.

Abstract P2789 – Table: ATD results

Rhythm/pacing site	SR	RA	VA	VOT	IVprox	IVdist	LVprox	LVdist	T
ATD[RVA-PLV] (ms)	112±34	111±33	168±65	99±27	46±40	60±76	-169±40	-159±76	75±101
Delta-ATD[RVA-PLV] (ms)	—	4±5	66±59	28±25	81±44	72±57	278±51	263±87	101±63
ATD[RVOT-PLV] (ms)	104±57	112±61	130±108	150±74	119±44	113±60	-152±39	-127±56	24±92
Delta-ATD[RVOT-PLV] (ms)	—	5±4	80±110	56±57	55±46	57±46	256±72	234±78	126±73

P2790 A simulation study to evaluate mechanisms underlying cardiac resynchronization therapy – Influence of delayed activation on regional deformation

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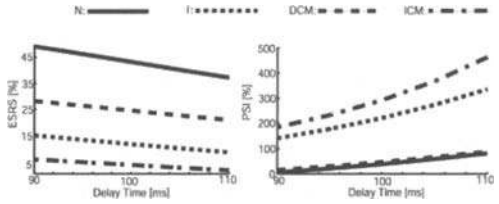
Background: The mechanisms underlying cardiac resynchronisation therapy(CRT) for ischaemic and non-ischaemic dilated myopathies is poorly understood. Both segmental ischaemia and delayed activation result in deteriorating regional stroke volume.
Study Aim: To study the influence of regional delayed activation times(DAT) on deformation in normal(N) and ischaemic(I) non-dilated hearts and in dilated(DCM) and ischaemic dilated(ICM) cardiomyopathies.
Model description: A mathematical model of a left ventricular midlevel short-axis slice was established to enable the description of radial deformation in interacting segments with heterogeneous (a)elasticity and (b)onset, magnitude and duration of active contraction. Ischaemia can be simulated by a reduced and prolonged active force. The active force always subsided before aortic valve closure(AVC). End-Systolic Radial Strain(ESRS) and a Post-Systolic Index(PSI), i.e. the thickening after AVC versus ESRS, were calculated. Typical end-diastolic diameters (N,I: 5 cm; DCM,ICM: 10 cm) and a range of delay times (90-110 ms) were extracted from patient data.
Findings: Both dilation and ischaemia reduced the ESRS, with a greater reduction in ischaemia, while PSI increased with ischaemia, but depended less on dilation (Fig. 1). ESRS decreased and PSI increased with increasing DAT. For dilated hearts ESRS is less influenced by DAT, with a further decrease for ischaemia. PSI depended significantly less on DAT for N/DCM than for I/ICM.



Conclusions: These findings suggest that segments with DAT and I/ICM would benefit less significantly from CRT to increase their stroke work. The same conclusion does not hold for DCM since for large ventricles a small increase in ESRS results in a significant increase in stroke volume.

P2791 Cardiac resynchronisation therapy tailored by echocardiographic evaluation of ventricular asynchrony

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Cardiac resynchronisation therapy (CRT) is a promising strategy in patients with severe heart failure (HF) and left bundle branch block (LBBB). However, no criteria are yet available to predict which patients will gain. The aim of this study was to investigate the value of inter- and intra-ventricular echocardiographic asynchrony parameters in predicting reverse remodelling after CRT.
We studied 20 patients (63±10 years, 8 male) with advanced HF (4 with ischemic and 16 with non-ischemic cardiomyopathy) and LBBB (QRS duration =>140 ms). Before pacemaker implantation, left ventricular asynchrony was assessed using echo-Doppler by calculating septal-to-posterior wall motion delay (SPWMD, i.e the shortest interval between the maximum posterior displacement of the septum and the maximum displacement of the left posterior wall during systole) and left ventricular electromechanical delay (LVEMD, i.e. the time between the onset of QRS and aortic flow). Inter-ventricular asynchrony (inter-ventricular delay, IVD) was evaluated by measuring the difference between the LVEMD and the right electromechanical delay (i.e. the time between the onset of QRS and pulmonary flow). Left ventricular end-diastolic (LVEDVI) and end-systolic (LVESVI) volume indexed for body surface area were calculated before and one month after implantation. The patients with a reduction in LVESVI >15% were considered responders.
CRT significantly improved LVEDVI (from 150±53 to 119±37 ml/m^2, p<0.001) and LVESVI (from 116±43 to 85±29 ml/m^2, p<0.0001). The responders showed a SPWMD significantly longer than non-responders (246±68 ms vs 110±55 ms, p<0.001). No differences were found between responders and non-responders in terms of QRS duration (173±18 ms vs 164±12 ms, p=NS), LVEMD (126±40 ms vs 163±55 ms, p=NS) and IVD (59±19 ms vs 73±21 ms, p=NS). All responders had a SPWMD > 130 ms. At this cut-off the specificity in predicting reverse remodelling was 63%, with a positive predictive value of 80% and an accuracy of 85%.
In conclusion, in patients with advanced HF and LBBB, baseline SPWMD is a strong predictor of the occurrence of reverse remodelling after CRT, thus suggesting its usefulness in identifying patients likely to benefit from biventricular pacing.

P2792 Improvement of cardiac efficiency by resynchronization therapy in dilated cardiomyopathy studied noninvasively with positron emission tomography

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Experimental investigations of our group had indicated adverse effects of both left bundle branch block (LBBB) and right ventricular pacing on cardiac efficiency that could be reversed by resynchronization (RT). Clinically, we examined the effects of RT by use of positron emission tomography (PET).
Patient characteristics and methods: 28 patients (pts) (11 females; age 63±7 y; EF 23±7%, NYHA class III; QRS duration 190±19 msec) with advanced DCM were studied before and 3-4 months after RT. PET data analysis: C-11 acetate clearance (k2-value; ~370 MBq C-11 acetate) was determined in a 1-compartment model as an index of myocardial oxygen consumption (MVO2). K2 (1/min) was related to individual rate-pressure product (RPP). In addition, myocardial blood flow (MBF) was measured quantitatively from C-11 acetate kinetics in a 20-segment model (polar maps) for parametric description.
Results: After RT mean K2-values of the left ventricle significantly decreased from 0.082±0.02 to 0.072±0.02 (p<0.001). Cardiac efficiency, estimated from pressure work related K2-ratio, increased by about 11.4%. Concomitantly, MBF related to RPP (7281±1709 vs. 8441±1985 after RT), decreased from 54±0.2 to 47±0.13 ml/min x 100 g (p<0.001) after RT. Regional MVO2 analysis of mainly involved regions (septal/lateral ratio) showed a normalization (1.0 vs. 0.83; p<0.01) after RT.
Conclusions: 1. RT improves cardiac efficiency in pts with DCM and LBBB estimated from noninvasive indices of pressure work and MVO2. 2. RT reversed inhomogeneity of regional MVO2 due to asynchronous contraction.

SIGNAL AVERAGED ELECTROCARDIOGRAM

P2793 P-wave signal-averaged electrocardiogram after successful cardioversion of acute and persistent atrial fibrillation

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A prolonged P wave in signal averaged high resolution ECG (P-SAECG) may indicate the presence of an impaired intra- and interatrial conduction, which could be a predisposing factor for atrial fibrillation (AF). The aim of the study was to evaluate the changes of P-SAECG in sinus rhythm restored in patients with different duration of AF.
Methods and Results: We evaluated 37 patients (29 males, age 62 ±12 y) after successful cardioversion (CV) of AF persistent more than one month (group A) and 20 patients (15 males, age 63±15 y) after CV of acute AF with duration less than 48 hours (group B). The control group consisted of 21 healthy subjects(11 males, 62±11 y) without history of AF and/or organic cardiac disease. We measured the filtred P wave duration and the root mean square voltage in terminal 20 ms of P wave (RMS 20), using the analysis of three orthogonal ECG leads (MAC 5000, Marquette). Left atrial diameter (LAD) and left ventricular ejection fraction (LVEF) were evaluated by 2D-echocardiography.
Results: Comparison of filtered P wave duration and LAD parameters for both AF patient groups is shown in the Table. Although filtered P wave duration was significantly longer and LAD significantly greater in group A as compared with control subjects, no such a difference was found between group B and controls.

Characteristics of group A and B

	Group A (n=37)	Group B (n=20)	P value
Age	62.2 ±12.1	63.0 ± 14.6	NS
LVEF (%)	57.4 ± 12.1	63.2 ± 5.9	NS
LAD (mm)	44.8 ± 6.2	37.5 ± 4.9	< 0.001
Mitral valve disease	10.8%	10.0%	NS
Amiodarone	27%	25%	NS
Propafenone	14%	20%	NS
P wave duration (ms)	173.0 ± 47.9	132.5 ± 21.1	< 0.001
RMS 20 (ms)	3.2 ± 1.8	4.2 ± 3.0	NS
Noise level (uV)	0.49 ± 0.20	0.44 ± 0.14	NS

Conclusion: Significant prolongation of the P wave duration in high resolution ECG after longer period of atrial fibrillation could reflect atrial electrophysiological remodeling caused by this tachyarrhythmia.

P2794 P-wave signal-averaged time domain parameters in interatrial septum pacing and dual site right atrial pacing

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Interatrial conduction disturbances (IACD) are the known substrate of re-entrant atrial arrhythmias and atrial pacing modes providing more symmetrical activation both of atria consist promising chance for this pts. The time domain of the signal-averaged (SA) P wave is considered as an easy and valuable method to investigate the electrophysiological properties of atrial myocardium. Promising results obtained previously by Padeletti and by us using only single site CS ostium region pacing inspired us for this study. Its aim was the comparison of influence of low-posterior interatrial septum pacing (IAS) and dual site (RAA+IAS) of right atrium pacing (DuRA) on SA P wave parameters.

Patients & methods: We examined 19 patients with dual site right atrial pacing system. Examinations were performed during IAS (SSI UP pacing program – cathode was connected to IAS lead) and DuRA pacing (SSI BP pacing program) 80 bpm. We analyzed the time domain of the signal averaged (SA) P wave from three orthogonal bipolar leads (XYZ) during pacing using both pacing modes. We considered three parameters: SA P wave duration, the root mean square voltage of the last 20 ms of SA P wave (RMS20) and the duration of oscillations lower than 5mV of the final part of the P vector magnitude (LAS5) as well as the presence of atrial late potentials (LP) criteria.

Results:

Parameters/average (SD)	IAS pacing	DuRA pacing	p
SA P wave duration	133.1(19.6)	131.2(15.8)	0.59
SA P wave RMS 20	3.2(1.21)	2.7(0.66)	0.06
SA P wave LAS 5	5.88(3.64)	6.13(4.3)	0.8
Atrial LP criteria*	4	5	-

*Atrial LP criteria–P wave duration > 125ms, RMS20<2,4mV, statistically significant p<0,05

The SA P wave time domain parameters analysis indicates, that there is no statistically significant differences between IAS pacing and DuRA pacing in the examined group of patients.

Conclusion: Low-posterior IAS pacing shows similar effects to DuRA pacing; it can to confirm utility this simple pacing mode for pts. with atrial arrhythmias.

P2795 Prognostic significance of serial P-wave signal-averaged electrocardiogram following electrical cardioversion of atrial fibrillation: a prospective study

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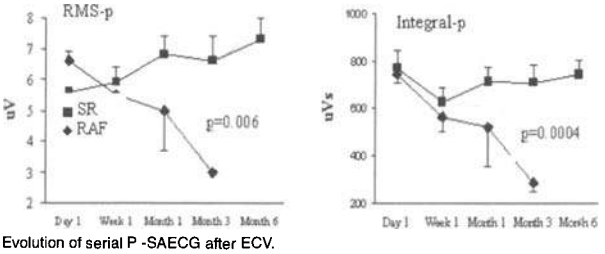
We hypothesise that the persistence of delayed atrial conduction detected by serial P-wave SAECG (P-SAECG) can identify pts who may recur atrial fibrillation (R-AF) after external electrical cardioversion (ECV). P-SAECGs were recorded on 60 pts after ECV for persistent AF(53 men, 66 ± 10 yrs) and repeated on pts maintained sinus rhythm (SR) 1-week (w), 1-month (m), 3 and 6m later. Filtered P wave duration (PD), RMS of the terminal 40, 30, 20 ms (RMS-40, 30, 20) of the filtered P wave, RMS of the entire filtered P wave (RMS-P) and the integral of voltages in entire P wave (integral-p) were obtained from each recording. Of 60 pts, 31(52%) returned to AF within 1w, 11(18%) between 1w and 1m, 2(3.3%) between 1 and 3m and 2(3.3%) returned to AF between 3 and 6m. There were no significant differences between pts with(n=46) and without R-AF(n=14) in clinical variables except AF duration. The pts with R-AF had longer PD (157±24 vs. 143±17ms, p<0.0001) and lower RMS-40, RMS-30, RMS-20 (5.3±2 vs. 6.1±3.4 μV; 4.3±1.5 vs. 5.7±3.2 μV; 3.6±1.4 vs. 5.2±3 μV, all p<0.007, respectively) than pts with SR. Above 4 indices did not change significantly over time, however the RMS-p was increased in SR pts (p=0.009) whilst a reduction was noted in R-AF group(p=0.032), integral-p was only decreased in R-AF group (p=0.0028). In RMS-P and integral-p (Fig) the difference between SR and R-AF slopes were significant.



Evolution of serial P -SAECG after ECV.

The inclusion of dynamic changes in PD and RMS-p in the 1w recording in the definition of an abnormal P-SAECG provided improved predictive power compared to analysis of the P-SAECG at day 1 alone. Sensitivity for detecting R-AF between 8-30 days was increased from 72.7 to 100% and positive predictive accuracy from 72.7 to 84.6%.

Conclusion: Serial P-SAECG following ECV can be used to predict AF recurrence.

P2796 Late potentials in patients with acute myocardial infarction treated with thrombolytic therapy-are they predict the long-term prognosis?

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Background: Signal averaged ECG is useful non-invasive tool for detecting patients at risk for sudden cardiac death after acute myocardial infarction. The aim of the study was to estimate prognostic significance of ventricular late potentials in pts with AMI treated with thrombolytic therapy during the long-term follow-up.

Method: The 281 pts with AMI treated with intravenous streptokinase and discharged alive were followed-up to 10 years. There were 85% male, mean age 55 ± 9 years (range 32-77). Signal-averaged ECG was performed within 1 month after AMI. Late potentials were considered positive if 2 of 3 criteria were found. Positive LPs had 52 (18.5%)-group I, and negative LPs 229 (81.5%) pts-group II. There were no significant differences between groups in gender, age, history of diabetes, previous infarct, QRS score, Killip class, peak CPK level, left ventricular end-systolic volume and ejection fraction.(p=NS). Patients with positive LPs had a higher mean end-diastolic volume (p<0.02), as well as more occluded IRA (p<0.03) than those with negative LPs.

Results: During 10-year follow-up 67 (23.8%) pts died: 22 in group I and 45 in group II, (42.3% vs. 19.7%, p<0.0005). A half of all deaths were sudden cardiac deaths (SCD), 34/67 (51%). SCD was recorded in 11 pts with positive and 23 pts with negative LPs (21.1% vs.10.0%, p<0.05). Actuarial curves comparing all cause death-free survival in those groups were estimated. There was significant difference between groups I and II after 16, 32, 48, 64, 80, 96 and 108 months, respectively: 88.5% vs. 96.5%; 78.8% vs. 93.9%; 76.9% vs. 91.7%; 66.8% vs. 88.5%; 64.5% vs. 83.8%; 61.6% vs. 78.8%; 54.8% vs. 77.2%. (p<0.000). Likewise, actuarial curves comparing SCD-free survival differed significantly between groups I and II after 16, 32, 48, 64, 80, 96 and 108 months, consecutively: 94.0% vs. 98.2%; 87.8% vs. 96.4%; 85.6% vs. 95.9%; 83.3% vs. 94.6%; 80.3% vs. 91.2%; 80.3% vs. 89.1%; 75.8% vs.87.3%.(p<0.02)

Conclusion: Presence of positive LPs in patients with acute myocardial infarction treated with thrombolytic therapy is a significant predictor of sudden cardiac death and overall mortality during long-term follow-up. Patients with positive LPs had more occluded IRA and higher mean EDV.

P2797 Late potentials in arrhythmogenic right ventricular cardiomyopathy: long-term follow-up

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The aim of our study was to evaluate the modifications of late potentials during a long-term follow-up in patients with arrhythmogenic right ventricular cardiomyopathy, and to compare these results with the echocardiographic findings during the same period. We studied 20 consecutive patients (12 males, 8 females) with a mean age of 27±14yrs. After the baseline visit, all of them were followed by outpatients controls every 2 years until 8 years. At each visit they underwent signal averaging ECG and echocardiography with measurements of left and right ventricle volumes and ejection fractions. The two filter settings considered showed a similar behaviour, with a progressive increase of late potentials through alternate phases of increment and reduction (table). Echocardiographic indexes did not show significant modifications during follow-up.

Signal-averaging ECG parameters

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
5O-250Hz					
QRS	127±12	133±11	127±13	128±13	135±19
HFLA	26±10	26±11	27±12	28±10	31±14
RMS	59±57	38±20	51±50	43±35	40±31
40-250Hz					
QRS	119±15	127±16	122±16	121±12	128±19
HFLA	38±13	43±18	42±14	44±12	48±21
RMS	27±16	21±16	22±16	21±16	19±12

Values are expressed as mean ± standard deviation. QRS: filtered QRS duration; HFLA: high frequency low amplitude signals duration in the terminal portion of QRS; RMS: root mean square voltage in the last 40ms of the filtered QRS.

In conclusion, signal averaged ECG puts in evidence a progressive extension of zones with delayed conduction, that is not related with noticeable modifications detectable by echocardiography. Transient reductions of late potentials could reflect the formation of compact fibrotic/fatty tissue, with a complete substitution of myocardial fibres with delayed conduction.

P2798 Prognostic value of the signal-averaged P-wave for the recurrence of atrial fibrillation after successful cardioversion

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The aim of this prospective study was to assess the prognostic value of the signal-averaged p wave for the recurrence of atrial fibrillation (AF) after successful electrical cardioversion (CV). In 57 patients (11 women, 46 men; mean age 61 years) who had had sinus rhythm(SR) restored the day before, a signal-averaged ECG of the p wave was recorded and analysed using unidirectional, bidirectional and FIR filters. Four weeks and 12 months later, all patients were evaluated for the recurrence of AF.

Results: After cardioversion, 10 pts (18%) had a normal p wave <138.5 ms in the signal averaged ECG. Four weeks later, 22 pts (39%) had atrial fibrillation; their mean p wave duration in the first signal-averaged ECG had been 157 ms. The 34 pts who still remained in SR had had a mean p wave duration of 148 ms (P=0.07). Kaplan Meyer graphs of the AF recurrence-free periods over the entire 12-month-interval show overlapping curves of the two groups with normal and prolonged p wave durations (log rank test: P=0.62). Results were comparable when bidirectional and FIR filters were used, including parameters like root mean square voltage.

Conclusion: In spite of a tendency towards longer p waves in the AF recurrence group, the signal averaged ECG of the p wave is not a useful method to predict the recurrence of atrial fibrillation in patients after successful electrical cardioversion. Only a small proportion of signal averaged p waves qualifies as "normal" after a period of atrial fibrillation and consequent electrical cardioversion.

P2799 Transcoronary ablation of septal hypertrophy for HOCM. No evidence for the induction of an arrhythmogenic substrate

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Transcoronary ablation of septal hypertrophy (TASH) is a catheter interventional therapy for HOCM. However, for reduction of septal thickness, elimination of outflow obstruction and improvement of symptoms, the injection of 96% ethanol (2.6±1.6 ml) into a septal branch as well as the induction of a septal necrosis (~3% of the left ventricular mass) had to be accepted. Consideration had to be given predominantly to the possibility of the induction of an arrhythmogenic substrate with subsequently enhanced risk of sudden cardiac death.

To evaluate the influence of TASH on the signal-averaged ECG (SAECG) a time domain analysis was performed in 30 consecutive pts. (17 men, 51±16 y., prior syncope in 11) with sinus rhythm and normal intraventicular conduction before and after intervention. The results were correlated to haemodynamic and electrophysiologic parameters including programmed ventricular stimulation (PVS) at 2 right ventricular sides with up to 3 extrastimuli. Clinical information is obtained with a max. of 68 months after TASH (average 37±16 months).

Two weeks and six months after septal infarction the QRS duration (from 102±12 to 101±20 to 100±10 ms), the amplitude in the last 40 ms of the filtered QRS-complex (RMS) (from 69±44 to 61±41 to 63±42 μV) and the duration of late potentials (LAS) (from 26±9 to 26±10 to 25±8 ms) remained unchanged despite a peak CK-activity of 453±227 U/L induced. Furthermore, with regard to the Simson rules 25 out of 27 initially "late potential negative" pts. remained without evidence for a newly developed abnormal SAECG. This was accompanied by a lack of inducebility at PVS in all pts. investigated. During follow up non of the 30 pts. enrolled suffered an arrhythmogenic event like sustained ventricular arrhythmia or death.

Conclusion: With regard to time domain analysis of the signal-averaged ECG a TASH induced septal necrosis remained without evidence for the induction of an arrhythmogenic substrate. However, further investigations and a longer follow up in a larger number of pts. are needed.

SUDDEN DEATH – RESUSCITATION

P2800 Dispatch delay of first responders in out-of-hospital cardiac arrest limits its benefit

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Objective: Early defibrillation by first responders can significantly improve survival of out-of-hospital cardiac arrest. For early defibrillation travel-time of the first responder but also the rapid dispatch is crucial. We analyzed the functioning of the dispatch system in the Netherlands.

Methods: Medical calls to the central alarmnumber 112 are directed to the emergency medical system (EMS) dispatch center (DC). When the EMS DC receives a call concerning a cardiac arrest, 2 ambulances are sent and the police or fire DC, depending on the region, is alarmed. The police or fire DC directs a police patrol or fire engine with AED to the scene. All relevant time points and time intervals, corrected to a standard clock, were obtained from interviewing of witnesses at the scene, the system information of the DCs and the time registration of the defibrillators.

Results: 479 bystander-witnessed cardiac arrest were analyzed. In 138 calls a fire engine and in 341 calls a police patrol was dispatched as first responder. In the table the time intervals of dispatching the EMS and first responder are shown.

	EMS	Police	Fire fighters
Collapse to call EMS	120 (60-224)	120 (60-210)	120 (60-240)
Call EMS to call first responder DC	N/A	120 (60-189)	154 (81-271)
Call first responder DC to dispatch first responder	N/A	60 (0-60)	60 (60-127)
Call EMS to dispatch	120 (90-180)	184 (120-274)	259 (183-360)
Driving time	300 (240-435)	180 (120-300)	180 (120-261)
Collapse to arrival	607 (480-818)	540 (411-720)	632 (519-855)
Arrival at the scene to shock (in case of VF)	144 (86-225)	125 (77-186)	130 (74-180)

Time interval in seconds, median (25%-75%)

Conclusion: Driving time of first responders is very short, but much time is lost in decisions in EMS dispatch centers and in communication between dispatch centers. To optimize a first responder project separate dispatch centers must integrate and speed up dispatch decisions.

P2801 Sudden death in children and young adults: still cases of unknown cause

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Aim: Aim of the study was to investigate the causes of sudden death (SD) in the young in a representative Greek population.

Methods: We recorded consecutive cases of SD in children and young adults(1-35 years) in the region of Attica and Cyclades during a 4-year period and identified the cause of death according to pathological examination.

Results: We recorded 130 consecutive cases of SD. Eighty-nine (69%) were males (mean age 27.0±8.6 yrs) and 41 (31%) females (mean age 24.3±10.0 yrs) (p=0.11). SD was of cardiovascular origin in 96 (74%) cases. In 29 (22%) cases, the cause of SD remained unknown despite detailed pathological investigation. In 37(28%) cases, SD occurred at age range 1-20, while in 93(72%) cases in age between 21-35 years. In age group 1-20, the most frequent cardiac cause of SD was hypertrophic cardiomyopathy (HCM) (9 cases, 24%). In age group 21-35, atherosclerotic coronary artery disease (CAD) was the leading cause of SD (26 cases, 28%). In males, atherosclerotic CAD was the most frequent cause of SD (25 cases, 28%). In females, the majority of SD cases was of unknown cause (12 cases, 29%).

Causes of sudden death

Causes of SD	SD cases (%)
Cardiac causes	80 (62%)
– Atherosclerotic CAD	27(34%)
– HCM	16(20%)
– Congenital heart disease	12(15%)
– Myocarditis	4(5%)
– Dilated cardiomyopathy	4(5%)
– Unclassified cardiomyopathy	3(4%)
– Naxos disease	2(2%)
– Arrhythmogenic right ventricular cardiomyopathy	1(1%)
– Myocardial ischemia	1(1%)
Vascular causes	16(12%)
Non-cardiovascular causes	5(4%)
Unknown cause	29(22%)

Conclusions: SD in children and young adults is of cardiovascular origin in the majority of cases. A considerable number of SD cases in the young remain of unknown cause despite detailed investigation, especially in females. There is a preponderance of male gender in the SD young population.

P2802 Prolonged cardiopulmonary resuscitation should be not a contraindication for the thrombolytic therapy in acute myocardial infarction

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Background: Taking into consideration a potential risk for internal bleeding, the ACC/AHA and the ESC guidelines consider prolonged or traumatic cardiopulmonary resuscitation (CPR) as a relative contraindication for thrombolysis in acute myocardial infarction (AMI).
Objective: Safety and efficacy of thrombolysis in a group of patients (pts.) with AMI and prolonged CPR have been studied.
Methods: In a group of 946 consecutive pts. with ST segment elevation AMI treated with thrombolysis (Streptokinase 1.5 MU/20-60 min.) within the first 6 hours after the onset of the chest pain we identified 51 pts. (18 females, 33 males, age 62±12) who underwent more than 10 min. of CPR. CPR was performed by a trained personnel according to the European Resuscitation Council,s (ERC) Guidelines for basic and advanced life support.In 18 pts. CPR was performed before, in 20 pts. during and in 13 pts. immediately after thrombolysis. Sixteen pts. (39%) were in Killip class I, 10 pts (24.4%) in class II, 7 pts (17.3%) in class III and 8 (18.5%) in class IV. All pts. who survived received aspirin and heparin 1000 i.u./hour, 48-72 hours. Autopsy was performed in all pts. who died. The incidence of the minor and major haemorrhagic events have been evaluated.
Results: The average time of CPR was 26 ±15 min. (limits: 10-60 min.). Seventeen pts. (33.3%) survived. Major bleeding was registered in 4 pts. (9.2%) (hemathemesis in all 4) but this complication was not a cause of death. Minor bleedings were registered in 8 pts. (18.5%). No stroke was registered in this group. Autopsy performed in the 34 pts. who died did not show any sign of serious intra thoracic or intra abdominal bleeding.
Conclusions: Prolonged CPR performed in pts. thrombolised for AMI according to the ERC Guidelines does not increase the risk for serious internal bleedings. Our data suggest that prolonged CPR should be not considered as a contraindication for the thrombolytic therapy.

P2803 Epidemiological pattern and prediction of sudden cardiac death after myocardial infarction in patients with optimized beta-blocking therapy

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Background: Data from various sources have shown that one half of cardiac deaths are sudden occurring mostly within the first year after an acute myocardial infarction (AMI), and that some arrhythmia risk variables are able to predict the occurrence of sudden cardiac death (SCD). We studied whether the prediction and epidemiological pattern of SCD will change, if the medical therapy of the patients is optimized according to contemporary guidelines after the AMI.
Methods and Results: A consecutive series of 700 patients (mean age 62± 10years, 182 females and 518 males) with an AMI was included in this single-center, prospective follow-up study. The end-points were non-SCD, SCD, and arrhythmia events. Arrhythmia risk variables, such as non-sustained ventricular tachycardia (VT), heart rate variability, baroreflex sensitivity, signal averaged electrocardiogram (SAECG) and QT dispersion were analyzed among the patients who were discharged alive from the hospital (n=675). Cardiac medication was optimized according to contemporary guidelines with special emphasis on the implementation of long-term beta-blocking therapy, which was used by 97% of the patients at the time of discharge from hospital and by
95% at one year after the AMI, respectively. During the mean follow-up of 40±14 months, 34 non-sudden (5.0%), and 19 sudden (2.8%) cardiac deaths occurred, and 15 patients had an arrhythmia event (2.2%). Only few SCDs (3/19, 16%) and arrhythmia events (3/15, 20%) occurred during the first 12 months after the AMI compared to non-SCDs (18/34, 53%) ($p<0.01$ for both). Most of the arrhythmia risk variables, e.g. non-sustained VT, QT dispersion, baroreflex sensitivity and SAECG predicted the occurrence of non-SCD ($p<0.05$ for all) but not the SCD (NS for all).
Conclusions: The epidemiological pattern of SCD is different from that reported earlier among the post-AMI patients in whom the beta-blocking medication has been optimized. The common arrhythmia risk variables seem to lose their power as predictors of SCD among these patients.

P2804 Death due to pulmonary embolism: a post mortem study

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Pulmonary embolism (PE) is reported to be the third commonest cardiovascular cause of death. Despite an increased awareness of the need for thromboprohylaxis, a significant number of deaths due to PE still occur without the condition being considered or recognised. We present the results of a post mortem review carried out as part of an epidemiological study into the incidence of PE in Southampton, UK (population of 430,408).
Over a one-year period from June 2000 to May 2001 all post mortem examinations performed in Southampton University Trust hospitals were reviewed for evidence of PE. 1164 post mortem examinations were performed during the study period, with evidence of pulmonary thromboembolism being identified in 87 cases, giving an overall post mortem incidence of 7.5% [95%CI, 5.96% - 8.98%]. Of the 1164 deaths, 668 were sudden or unexplained (57.4%), 514 of these occurring in the community (76.9%) and 154 in hospitalised patients (23.1%). PE was identified as the main or significant contributor to the cause of these sudden/unexpected deaths in 42 community and 20 hospital cases (8.2% and 13.0% of cases respectively).
PE remains a significant cause of death in the UK, both in community and hospital settings, despite an increased awareness and recommendations for the use of thromboprophylactic precautions. At post mortem, PE can be identified as the cause of almost 1 in 10 sudden or unexpected deaths.

P2805 Revascularisation after aborted sudden death: the most important treatment option for secondary prevention? Substudy from the LOHCAT trial

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Introduction: Life-threatening ventricular arrhythmias (VA) occur frequently in pts with coronary artery disease. The risk of recurrence of VA is according to the literature over 30% per year, so carefull evaluation is mandatory to determine the optimum treatment strategy for these pts. We prospectively evaluated the effects of revascularisation of survivors of sudden cardiac death. The Leiden Out of Hospital Cardiac Arrest Trial (LOHCAT) applies a standardized screening protocol in pts with VA.
Methods: The LOHCAT screening protocol includes: echocardiography, nuclear imaging, coronary angiography and an EP study. Pts with primary VF due to acute myocardial infarction (<48 hours) were excluded.
Results: From 1994 until 2001, 444 consecutive survivors of sudden cardiac death are included (350 male, 59±13 yrs, VF:235, VT:209). After evaluation coronary revascularisation was performed in 90 (20%) pts (45 pts CABG, 40 pts PTCA, 5 pts both CABG and PTCA). LV ejection fraction was 42±21%. Four pts died post operatively. All pts were inducible before revascularisation. The effects of revascularisation on inducibility of VT/VF were evaluated after the procedures with an EP study (37 pts were not inducible anymore). Before discharge, an ICD implantation was performed in 48 pts (56%) (3 underwent catheter ablation of VT as well) and one pt underwent catheter ablation of VT. Anti arrhythmic drugs were used by 36 pts. During follow-up (32±29 mos) 4 pts died (none of them due to VA). Recurrences were observed in 10 (12%) pts (9 with ICD back up, 5 shocks/pt, and one patient with AAD).
Conclusion: Revascularisation after aborted sudden death due to VA is a successful approach. The risk for recurrence decreases significantly to 12% in our study population during a follow-up of nearly three years. No patient died due to recurrent VA.

P2806 Age-dependency of various causes of sudden cardiac death in the young

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Objective: The aim of the present study was the establish the age-distribution of various causes of sudden cardiac death (SCD) in a series of young people (aged 1-35 yrs) who suffered cardiac arrest.
Design and Results. In the time interval 1980-2001, 317 (91 female and 226 male) consecutive cases of SCD in the young in Northeast of Italy have been prospectively studied according to a detailed pathology protocol as well as clinico-pathologic correlation. Cardiac arrest was mechanical in 21 (7%) due to aortic rupture (14), pulmonary embolism (5) or haemorrhagic shock (2). In the remaining 296 (93%) SCD was arrhythmic and major causes included atherosclerotic coronary artery disease (CAD 61,19%), arrhythmogenic right ventricular cardiomyopathy (ARVC 42, 13%), myocarditis (36, 11%), valve disease (31, 10%), conduction system disease (27, 8%), hypertrophic cardiomyopathy (28, 9%), congenital CAD (21, 7%), dilated cardiomyopathy (13, 4%), acquired non-atherosclerotic CAD (9, 3%) and postoperative congenital heart disease (5, 2%). In 23 cases (7%) no evidence of structural heart disease was found ("mors sine materia").
By ANOVA test a statistically significant difference in terms of mean age was found between subgroups of patients with different causes of SCD. In particular, mean age of patients who died suddenly due to atherosclerotic CAD was higher than that of patients with other cardiovascular substrates (29.8 vs 23.2 yrs, $p<0.0001$). We then subdivided the study population in four age-groups, ie group I <10 yrs(5%), group II 10-19 (19.5%), group III 20-29 (43.5%), and group IV 30-35 (32%), to analyze the distribution of various causes of SCD in the different age-intervals. In group I hypertrophic cardiomyopathy was the leading cause (25%) followed by congenital CAD (19%). In group II the leading cause was ARVC (18%) followed by congenital CAD (13%) and myocarditis (13%). In group III major causes of SCD were atherosclerotic CAD and ARVC (16% both). Atherosclerotic CAD was the leading cause in group IV accounting for 35% of all SCDs (vs 16% group III and none in group I and II).
Conclusions: The disorders responsible for SCD in children and adolescents are different from those in people older than 30 yrs. In the last segment of population, atherosclerotic CAD is by far the most common cause accounting for more than one-third of all SCDs. On the other hand children and adolescents die more often due to congenital abnormalities or myocarditis.

P2807 Sudden unexpected death in children with a previously diagnosed heart defect

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Objectives: the aim of the study was to identify all infants and children within the Netherlands with previously diagnosed heart disease who had a sudden and unexpected death (SUD), and to identify the possible cause of death.
Background: It is known that children with previously diagnosed heart defects die suddenly. The causes of death are often unknown.
Methods: All children (<19 years) with a previously diagnosed heart defect and SUD between January 1990 and June 2001 presenting to 7 of 8 tertiary centers in the Netherlands were identified using hospital databases. We excluded patients receiving compassionate care. Diagnoses, clinical status and circumstances of death were sought from casenotes and postmortem reports. Deaths were classified as of cardiac or non-cardiac origin.
Results: We identified 150 cases of SUD (89 male) at a median age of 2.3years (18 days - 18.9 years); 49/150 patients (33%) were <1 year. Diagnostic categories included left to right shunts (N=34, 14 <1 year), cyanotic lesions (N=38, 13 <1 year), cardiomyopathy (N=11, 2 <1 year), univentricular heart (N=24, 10 <1 year), obstructive lesions (N=11, 3 <1 year), primary arrhythmia (N=8, 0 <1 year), and miscellaneous defects (N=18, 5 <1 year). 108 of 150 patients (72%) had been operated of whom 61 (57%) had had corrective surgery. Of the infants with SUD, 32/49 (65%) had undergone surgery (11 corrective); 76/101 older children had undergone previous surgery (50 corrective). 114 of 150 children (76%) died of a cardiac cause. Causes of death were arrhythmia (59), heart failure (25), shunt occlusion (10), pulmonary hypertensive crisis (8) and acute myocardial infarction (4). 30 of 49 infants died of a cardiac cause; causes of death included arrhythmia (10), heart failure (8), shunt occlusion (7), acute myocardial infarction (2).
Conclusions: The incidence of SUD in children with previously recognised heart defects is low. The majority of deaths were of cardiac origin. Pump failure and arrhythmias were terminal events in a significant number of patients in the entire population.

P2808 Advanced cardiac life support training does make a difference

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Many factors influence the success of in-hospital cardiopulmonary resuscitation (CPR). This multicenter, prospective study examined how Advanced Cardiac Life Support (ACLS) training influenced CPR outcomes in 156 patients who experienced 172 in-hospital cardiorespiratory arrest (CRA) events from 01/98 to 03/01. Rates of return of spontaneous circulation (ROSC), short-term survival (alive at hospital discharge), and long-term survival (30 days and 12 months) were compared between two patient groups: "With ACLS" (at least one team member had ACLS training) and "Without ACLS" (no team member had ACLS training). The ROSC rate was 37.8% (65/172) for all events and 39.7% (62/156) for all patients. This rate was 43.4% (49/113) versus 27.1% (16/59) in the "With ACLS" and "Without ACLS" groups, respectively ($p=0.037$). Hospital discharge rates were 22.1% (21/95) and 1.2% (5/49), respectively ($p=0.08$). After one year, 9.6% (15/156) of patients, all from the "With ACLS" group, were alive. Other factors related to survival included the event site, immediate cause, initial rhythm, duration of care, prior presence of oral-tracheal intubation, and need for a transcutaneous pacemaker. In conclusion, we found that the presence of at least one ACLS-trained team member doubles the chances of ROSC, thus, increasing the chances of survival until discharge.

P2809 Psychological stress in lay defibrillation: cognitive and emotional aspects

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Objective: The emotional and cognitive effects on persons in defibrillation teams and the opinion of the patients treated by these first responders were analysed for the first time in a prospective study.
Methods: After training in CPR and semiautomatic defibrillation, members of 36 different fire-brigades in the region of Olten (Switzerland) act in AED-teams as first responders in cardiac emergencies. At the beginning of the study relevant psychological and social aspects were analysed; after interventions, the participants were questioned on the emotional situation regarding coping, causal attribution and stress. Furthermore, in a parallel case-control study, survivors of cardiac emergencies were interviewed immediately upon hospitalisation and questioned in a semi-structured way on the emotional strain caused by intervention of the AED-team in comparison with the intervention of the regular ambulance team.
Results: 369 members of AED-teams participated in this study (78% of all members; mean age 36 years, 86% men). Duration of observation was 8±6.5 months. On average, 6±3.5 interventions/ defibrillations were made by the team members. At the beginning of the study, 32% expressed fear to make a mistake during the intervention/defibrillation; after there interventions the percentage was down to 9% ($p<0.01$). 79% considered a persisting fear to be confronted with friends/family during an intervention as the main subjective stress factor. After an intervention, the AED-team-members were often preoccupied with the fate of the relatives of the patient (86%). 14% of the men and 34% of the women ($p<0.01$) were preoccupied with the intervention/ defibrillation for at least 30 minutes and up to <24h; 7% of them were preoccupied for more than one day. 36% of the women and 16% of the men ($p<0.01$) considered discussing the case within the team to be the most effective coping strategy. Women expressed significantly more fear to fail (16% vs. 34%; $p<0.01$).
64 patients were questioned after intervention of the AED-team (control group n=61) and noticed no difference between a AED-team or a regular ambulance team regarding emergency intervention and care.
Conclusion: Out-of-hospital defibrillation causes acceptable levels of psychological stress in AED-teams. Women suffer more emotional stress than men and use different coping strategies. The integration of laypersons into defibrillation-teams is well accepted by patients.

GROWTH FACTORS AND CELL PROLIFERATION IN ATHEROSCLEROSIS

P2810 Regulation of vascular cell phenotype by the cell adhesion glycoprotein T-cadherin

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Cadherins are calcium-dependent surface adhesion molecules that engage in homotypic cell-cell adhesion and regulate morphogenesis and tissue architecture. T-cadherin (T-cad), an unusual GPI-anchored cadherin family member, is highly expressed in cardiac and vascular tissue, but its function in these tissues is unknown. Our immunohistochemical studies in healthy and diseased (i.e. human atherosclerosis, experimental restenosis) blood vessels suggest that expression levels of T-cad might correlate with phenotypic modulation. We hypothesize that T-cad plays an important role in the control of vascular architecture, and have examined the function of T-cad with respect to regulation of vascular cell phenotype.

Methods: Human umbilical vein endothelial cells (HUVEC) and human aortic smooth muscle cells (HSMC) were cultured in the presence of anti-T-cadherin antibodies (ab's). Parameters studied were cell morphology, adhesion and proliferation. HEK293 and L929 cells stably transfected with human T-cad were examined in parallel.

Results: T-cad transfected cells showed significantly reduced proliferation and migration rates (vs. parental and mock-transfectants). Anti-T-cad ab's exaggerated these characteristics, implying an agonistic effect of the ab's. When cultured on a substratum of anti-T-cad antibodies (vs. control surface) HUVEC change from a cobble-stone to an elongated "angiogenic" morphology, while HSMC exhibit a less "spread" morphology and form patchy monolayers. Phalloidin staining revealed associated redistribution of the cytoskeleton to a distinctly peripheral location. HUVEC and HSMC adhesion on anti-T-cad ab-coated substratum is significantly reduced as compared with cells seeded onto uncoated or gelatin-coated surface. When seeded onto a monolayer of stably T-cad-transfected L929 cells, adhesion of HUVEC and HSMC is also significantly reduced as compared to adhesion on a mock-transfected L929 monolayer. Studies are ongoing to determine signalling pathways through which T-cad mediates its effects on cell phenotype.

Conclusion: Homophilic T-cad-T-cad interactions influence the morphology/phenotype of vascular cells. The findings of anti-adhesive properties for T-cad may be relevant to a function for this molecule in negative guidance and definition of tissue architecture.

P2811 VEGF and bFGF upregulates endothelial nicotinic acetylcholine receptor

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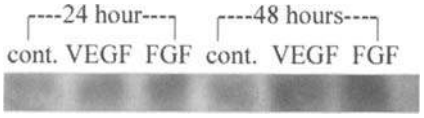
Background: Recently, we have made the novel and serendipitous observation that nicotine is an extraordinarily potent agent of angiogenesis. Nicotine's action, however, seems to be accentuated in sites where vascular abnormalities are present. For instance, using a rat hindlimb ischemia model, we observed that nicotinic acetylcholine receptor (nAChR) is upregulated in vascular tissues from the ischemic leg when compared against the nonischemic leg from the same rat. Accordingly, we sought to determine whether vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), both of which are upregulated by ischemia, could modulate the expression of endothelial nAChR.

Method: HMEC-1, an immortalized human dermal microvascular endothelial cell line was cultured in M199 supplemented with 10% FBS and antibiotics. At subconfluence, 10 ng/mL of VEGF and bFGF were given to HMEC-1. At 24 and 48 hours, cells were lysed and centrifuged. The supernatant was heated at 100°C for 5 minutes and used for Western blotting. Hybond ECL nitrocellulose membranes with proteins transferred from SDS-PAGE gels were incubated with a mouse monoclonal antibody (1:3000) raised against human nAChR alpha-7 subunit. The membrane was then probed with a peroxidase-conjugated anti-mouse antibody (1:2000), detected by ECL.

Result: VEGF and bFGF both upregulated endothelial nAChR within 24 hours. The effect became more conspicuous by 48 hours (Figure 1).



Conclusion: We have demonstrated that VEGF and bFGF are both determinants of endothelial nAChR expression. Henceforth, they can both modulate endothelial sensitivity to nicotine and thus play a major role in the angiogenic pathway mediated through nAChR.

P2812 Short-term exposure of vascular smooth muscle cells (VSMC) to a contrast medium-paclitaxel formulation inhibits proliferation in vitro

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Objective: Contrast media (CM) may be novel carriers suitable for intracoronary local drug delivery. This concept is based on the observation that CM form a thin film lining the endothelial surface of a coronary artery over a period of several minutes after bolus injection. A drug with high affinity to the tissue admixed to CM could be delivered at high concentrations to a dilated or stented artery for prevention of restenosis. Systemic drug levels are expected to remain far below toxicity due to rapid dilution after passage through the coronary arteries.

Methods: For investigation of the efficacy of an Iopromide-Paclitaxel formulation we seeded VSMCs at 10,000/cm^2 and incubated them with medium containing additives of either 0.9% NaCl (control), or Iopromide admixed with 25.7 μg/ml Paclitaxel. These specific media were replaced after 60 minutes, 10 minutes, or 3 minutes by neutral media not containing antiproliferative drugs. Cells were further cultivated for 12 days and counted at baseline, and after 3, 6, 9, and 12 days.

Results: The Iopromide-Paclitaxel formulation inhibited VSMC proliferation at all time points significantly (p=0.01). Incubation times of 10 and 3 minutes showed the same efficacy as an incubation over 60 minutes.

Relative increase in cell density

	day 0	day 3	day 6	day 9	day 12
saline	1.0	3.2	6.4	7.2	7.9
60 min	1.0	0.9	1.3	1.5	1.3
10 min	1.0	0.9	1.0	1.0	1.6
3 min	1.0	1.0	1.1	1.2	1.0

SEM < 10%, n=40

Conclusion: Iopromide-Paclitaxel formulations induce inhibition of VSMC proliferation. This effect is sustained over 12 days despite of the short initial exposure time. These data support the concept of CM-based coronary local drug delivery for prevention of restenosis.

P2813 The biomechanically-induced product of the IEX-I gene inhibits proliferation of vascular smooth muscle cells

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Mechanotransduction participates in both physiological and pathological processes of the cardiovascular system.

We investigated biomechanically-induced changes in gene expression of cultured human aortic smooth muscle cells (hAoSMC) obtained from human surgical specimens. Using microarray techniques, we identified the irradiation-inducible gene IEX-I as highly expressed in hAoSMC in response to mechanical strain. This finding was confirmed by Northern analysis (maximal induction after 2 hrs; 15 fold induction) and Western analysis (maximal induction after 24 hrs; 3 fold induction). Moreover, expression of IEX-I in hAoSMC was induced by the proinflammatory cytokine IL-1beta (24 hrs; 5 fold induction). The function of IEX-I in hAoSMC was further explored by gene transfer with recombinant adenoviruses that overexpressed wild-type IEX-I. Proliferation of hAoSMC was monitored by ^{3}[H]-thymidine incorporation. After 48 hrs of 4% mechanical strain, adGFP-infected hAoSMC had higher ^{3}[H]-thymidine incorporation as compared to adIEX-I-infected cells (13455±4211 vs. 4733±1121 counts per μg, p<0.001). In addition, proliferation of hAoSMC induced by a combination of PDGF-BB and FGF-2 was reduced by 46% in adIEX-I-infected cells as compared to adGFP-infected SMC (p<0.001).

In an in vivo study of ApoE-/- mice, immunohistochemical staining of carotid arteries using a specific anti-IEX-I antibody revealed strong immunoreactivity in the arterial wall of animals on a high-fat diet as compared to weak staining in vessels from mice on a low-fat diet. In addition, significant immunoreactivity for IEX-1 was found in human carotid atheroma specimens demonstrating an increased expression of this protein in human atherosclerosis.

In conclusion, our findings demonstrate that mechanical strain induces IEX-1 and that the protein product of the IEX-1 gene is overexpressed in diseased vessels. Because IEX-1 has distinct antiproliferative effects in hAoSMC, this novel gene may participate in regulating the vascular response to injury.

P2814 Differential roles for Src, PI-3 kinase and PLC-gamma for platelet-derived growth factor (PDGF)-alpha receptor-induced chemotaxis

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Platelet-derived growth factor (PDGF) plays a critical role in the pathogenesis of atherosclerosis and myocardial hypertrophy. Our previous work demonstrated, that activation of multiple receptor-associated signaling molecules including Src, PI-3 kinase (PI3K) and PLCg is essential for efficient PDGF-AA-induced chemotaxis. Cell migration requires the coordinated interplay of several cellular responses including motility, invasiveness and polarization.

Here we investigated the differential roles for Src, PI3K and PLCg for PDGF-dependent induction of chemotaxis-associated transcription factors (Egr-1, Ets-1, c-fos) and the ligand-induced internalization of the alpha-PDGF receptor (aPDGFR). To investigate the role of each of these signaling enzymes, we used mutant receptors in which the specific binding sites for Src, PI3K and PLCg were individually deleted by tyrosine-to-phenylalanine substitutions. Stimulation of Ph cells expressing the wild type (WT) aPDGFR with PDGF-AA (50 ng/ml) led to a 10-fold increase of Egr-1, Ets-1, and c-fos at 60 min, and to a rapid internalization of the receptor at 5 min. Deletion of the binding sites for PI3K and PLCg, but not Src, each led to a 50% reduction of PDGF-dependent induction of Egr-1, Ets-1, and c-fos (mRNA, protein; $P<0.01$). In contrast, deletion of the Src binding sites, but not PI3K and PLCg, completely abolished the ligand-induced internalization of the aPDGFR. Consistent with these findings, restoration of the individual binding sites to a mutant receptor, in which all binding sites were deleted (F7), rescued these responses.

We conclude that redundant signaling pathways involving PI3K and PLCg mediate the PDGF-dependent induction of Egr-1, Ets-1 and c-fos, whereas Src family kinases are required for aPDGFR internalization. Only the coordinated interplay of these cellular responses allows an efficient migratory response towards PDGF.

P2815 IGF-1 modulates cardiac fibroblast migration and adhesion through the expression and synthesis of α1, β1-integrin and collagen

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The extracellular matrix (ECM) composition and organization change during periods of cardiac tissue remodeling associated with development, aging and disease. Cardiac fibroblast interaction with the surrounding ECM is dynamic and essential for regulation of adhesion and migration. Whether IGF-1 regulates these processes in cardiac fetal and neonatal fibroblasts remains unknown.

Our aim was to evaluate if IGF-1 regulates cardiac fetal and neonatal fibroblast migration and adhesion and its relation with changes in collagen and integrin expression. Fibroblasts isolated from rat fetal and neonatal hearts were stimulated with IGF-1 and cell adhesion and collagen gel contraction were evaluated. In addition, collagens and their specific integrin receptor levels were determined by Northern and Western blot analysis, respectively.

The results showed that fetal cardiac fibroblasts treated with IGF-1 increased significantly the contraction of collagen gels. Area decreases in collagen gels were 27 vs. 13 and 46 vs. 34% for IGF-1 vs controls, at 24 and 48 h, respectively. In neonatal cardiac fibroblasts, IGF-1 did not produce any change on collagen gel contraction. IGF-1 increased cardiac fibroblast adhesion in 1.4, 1.3 and 1.5 fold over control, using collagen, laminin and fibronectin as substrates, respectively. IGF-1 decreased neonate fibroblast adhesion to collagen, laminin and fibronectin, in 0.8, 0.7 and 0.5 fold over control, respectively. IGF-1 stimulated collagen type-1 secretion in both fetal (1.5 and 1.8 fold over control at 24 and 48 h, respectively) and neonatal fibroblasts (1.9 and 1.4 folds over control at 24 and 48 h, respectively). IGF-1 treatment increased collagen mRNA levels in fetal and neonatal fibroblasts (1.4 and 7.0 fold over control at 24 h, respectively). IGF-1 also increased alpha1 and beta1 integrin levels (1.9-fold respect to control) in fetal fibroblasts. We concluded that IGF-1 differentially modulates cardiac fibroblast adhesion and migration in fetal and neonatal stages, regulating both collagen type-1 synthesis and integrin expression.

P2816 The binding of the FVIIa to the TF promotes smooth muscle cell proliferation in vitro via the extracellular signal regulated kinases

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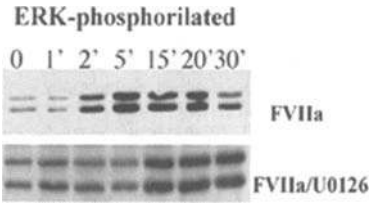
Restenosis following PTCA recognizes smooth muscle cell (SMC) proliferation as a key event. However, the mechanisms responsible for this phenomenon are not completely known. Tissue Factor (TF) is a transmembrane glycoprotein which forms a high affinity complex with Factor VII/FactorVIIa (FVIIa), thus activating the extrinsic coagulation pathway. Atherosclerotic plaques contain different cell types, such as SMCs, capable of expressing TF. We have previously demonstrated that binding of FVIIa to TF induces SMC proliferation. In the present study we investigated whether the formation of TF/FVIIa complex leads to SMC proliferation as a result of signal transduction via the extracellular signal regulated kinases (ERKs) pathway, a family of the MAPKs. SMCs from NZW rabbit aortas, grown in Dulbecco's Medium, with 10% Calf Serum, were made quiescent by serum deprivation. Twenty-four hours later SMCs were stimulated with FVIIa (100nM) and then processed for total protein isolation at baseline (no stimulation), and after 1, 2, 5, 15, 20, 30 and 60 min following stimulation. Phosphorylation (activation) of ERKs (pERKs) was assessed by immunoblotting SMC lysates with antibodies that recognize pERKs. To better define the role of pERK in SMC proliferation, in another set of experiments, SMCs were preincubated with U0126 (10μM), a specific inhibitor of ERK phosphorylation and then SMC proliferation and ERK phosphorilation were evaluated (figure).



SMC proliferation appears to be related to ERK phosporilation; UO126 was able to inhibit it. This effect was associated with the late phosporilation of ERK. Thus, TF/FVIIa complex leads to SMC proliferation via the activation of ERKs.

P2817 Severe diffuse coronary aneurysms in acute coronary syndromes are linked to altered serum levels of VEGF and TIMP2

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BaBackground: Coronary aneurysms and diffuse coronary ectasia (DCE) are found in Kawasaki syndrome, an inflammatory disease of the young. However, DCE can occasionally be found at angiography in adults without clinical features of Kawasaki disease. The pathogenesis of DCE in the latter is poorly known. Matrix metalloproteases (MMP), tissue inhibitos of MMP (TIMP) and vascular endothelial growth factor (VEGF) are involved in vascular remodelling and might play a role in DCE formation.

Methods: 1280 consecutive coronary angiograms, performed in 1999, were examined and DCE were found in 15 patients (14 male, age 56 years, range 40-64). They all presented with an acute coronary syndromes (8 with acute myocardial infarction, 7 with unstable angina). DCE were defined as >=1.5 fold increase in diameter with polyciclic margins of > 2 coronary segments out of 27 segments. Two patients died during the initial admission, 1 refused blood sampling; 12 patients remained stable and did not need revascularization. Plasma levels of VEGF, MMP2, TIMP1, TIMP2 and of C-reactive protein (CRP) were measured in these 12 patients, in 12 age/sex matched patients (CAD) with stable angina and critical stenoses (>50% reduction of internal lumen diameter) and in 12 age/sex matched patients (NCA) with normal coronaries admitted during the same timeframe.

Results: all data are presented as median and (range). No patient with DCE exhibited coronary stenoses. VEGF levels were higher in patients with DCE than in CAD or NCA: 151 pg/ml (30.1-382.2) vs 66.9 pg/ml (30.1-112.2) and 54.9 pg/ml (15.2-87), respectively, $p< 0.02$. TIMP2 levels were lower in DCE or CAD than in NCA: 5.9 ng/ml (0-182.2) and 5.0 (0-47.6) vs 50.7 ng/ml (0-101.3), respetctively, $p<0.001$. TIMP1 and MMP2 were similar in all groups (p=NS), and CRP was normal (<3 mg/L) in the majority of patients with DCE, CAD and NCA (75%, 66% and 84% respectively, p=NS)

Conclusion: In adults DCE are not associated with systemic signs of inflammation even when associated an acute coronary syndrome. Reduced TIMP2 was found both in CAD and DCE. Elevated VEGF, however, was only found in DCE. The simultaneous occurrence of deficient MMP inhibition and increased vascular permeability in adults with DCE suggest an accelerated extra-cellular matrix turnover faciling aneurysm formation.

P2818 Effect of overexpression of decorin on metalloproteinases and TIMPs production by human coronary artery smooth muscle cells

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Background: Metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are known to play a critical role in the Acute Coronary Syndromes. Additionally, the implication of pro-inflammatory cytokines (particularly TGF-beta) in regulation of MMPs has been previously demonstrated. Since decorin (small leucine-rich proteoglycan) is a natural inhibitor of TGF-beta and inhibits cell migration, we evaluated the direct effect of decorin overexpression on MMPs and TIMPs production by human coronary smooth muscle cells (SMC).

Methods and Results: Cultured human coronary artery SMCs (Clonetics, USA) were either infected with adenoviral vector containing human decorin gene (Ad-Dcn) or beta-Galactosidase (Ad-bataGal) at viral dose 25, 50, 100, 200 and 400 pfu/cell, or remained as uninfected culture controls. Four days after transfection, the supernatant of culture conditioned-medium was collected for protein analysis (decorin, MMP-1, MMP-2, MMP-3, MMP-9, MMP-13 and TIMP-1, TIMP-2, TIMP-3) by Western and dot blotting. Medium decorin concentration was significantly elevated from the viral dose 50 pfu/cell in Ad-Dcn infected-cells and no secreted decorin was detected in the supernatant of control cells. On dot blot, the protein level of MMP-1, MMP-3 and TIMP-3 diminished, respectively (1.4-, 2- and 1.6-fold) in Ad-Dcn infected-cells compared with control cells. In contrast, MMP-2, TIMP-1 and TIMP-2 showed a 1.3-, 1.5- and 1.2-fold increase in Ad-Dcn infected-cells. No significant difference was observed between decorin infected-cells and the control beta-gal cells in the protein level of MMP-9 and MMP-13 (they were not detectable in the uninfected cells). The similar data were obtained from Western analysis. Zymography confirmed the inhibition of MMP-3 activity and the stimulation of MMP-2. Total level of cytokines (TGF-beta, IL-1beta, IL-4, IL-6 and IL-10) in medium were also investigated by ELISA. In Ad-Dcn infected-cells, the level of TGF-beta, IL-1beta & IL-6 was reduced significantly in a dose-dependant manner compared with Ad-betaGal and control cells, whereas, the level of IL-4 & IL-10 was markedly increased.

Conclusion: Our preliminary findings suggest that decorin overexpression would have potential beneficial effect on atherosclerotic plaque stability via inhibition of MMP-1, 3 and stimulation of TIMP-1, 2.

P2819 Regulation of VEGF and its receptor in macrophages-effects of oxidized LDL and PPAR gamma agonists

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Increased vascularisation and inflammation in the atherosclerostic plaque may lead to destabilisation and rupture of the plaque. Vascular Endothelial Growth Factor (VEGF) and its receptor VEGFR-1 may play a central role in this development, since VEGF may promote formation of intraplaque microvessels and also is chemotactic for monocytes. The aim of this study was to investigate the effect of oxidised LDL (oxLDL) on VEGF and VEGFR-1 expression in human monocyte-derived macrophages. The VEGF and VEGFR-1 mRNA expression in these cells were estimated by RT-PCR and the VEGF protein secretion was measured by ELISA. Chemotactic activity was determined using a microchamber technique.

OxLDL increased the VEGF mRNA expression and protein secretion in a time and dose dependent manner. This was partly due to an increased VEGF mRNA stability. The gene for the VEGF receptor, VEGFR-1, encodes two polypeptides, a soluble (sVEGFR-1) and a membrane protein. The soluble form is supposed to block biological effects of VEGF, while the membrane bound form mediates the chemotactic response to VEGF. The mRNA expression of VEGFR-1, and protein secretion of sVEGFR-1 was decreased by oxLDL. Similar effects were obtained when cells were incubated with 9-HODE, which is a component of oxLDL and a physiological stimulator of PPAR-gamma. Similar results were also found with darglitazone, another PPAR-gamma agonist. The decreased VEGFR-1 mRNA expression coincided with a decreased binding of ATF-2/c-jun to the positive regulatory element, which is essential for VEGFR-1 gene transcription. Macrophages stimulated with oxLDL were less prone to migrate towards VEGF than untreated cells. Since chemotaxis of macrophages towards VEGF is mediated through the membrane bound VEGFR-1 this indicates a reduced expression of this receptor. Together these results indicate that oxLDL increases the amount of biologically active VEGF by increased VEGF secretion and a decreased secretion of sVEGFR-1. On the orther hand a decreased expression of membrane-bound VEGFR-1 in macrophages may contribute to entrapment of macrophages in the lesion.

P2820 Circulating human smooth muscle cell progenitors

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There is now accumulating evidence that smooth muscle cells contributing to vascular disease may originate from bone marrow-derived progenitor cells. Studies using human embryonic stem cells have also suggested a common vascular progenitor for endothelial and smooth muscle cells with evidence that cell lineage can be determined by differential growth factor exposure. However, despite substantial data to support the existence of circulating endothelial progenitor cells (EPC), no direct evidence currently exists for a distinct smooth muscle progenitor cell (SPC) in the blood stream of human subjects.

We evaluated whether growth and selection of adult vascular progenitors obtained from human peripheral blood in PDGF BB-enriched medium would result in smooth muscle cell differentiation. We determined the phenotype of these cells both morphologically and with use of a panel of cell specific antibodies.

Progenitor colonies obtained from human buffy coat mononuclear cells had a heterogeneous morphology consisting of polygonal endothelial-like cells and stellate shaped smooth muscle-like cells. Passage and selection of these mixed colonies in either PDGF or VEGF enriched medium resulted in pure cultures of smooth muscle (SPC) or endothelial (EPC) appearing cells respectively.

SPCs stained positive for alpha smooth muscle actin, smooth muscle myosin heavy chain (SM MHC) and calponin on indirect immunofluorescence, whereas EPCs stained negative for these smooth muscle cell markers. Conversely, EPCs were positively immunoreactive for vWF, VE-cadherin, CD31 and CD36, whereas SPCs showed no expression of these endothelial antigens. Smooth muscle specific protein expression by SPCs was confirmed by positive immunolabeling for alpha smooth muscle actin, SM MHC and calponin on Western blots of SPC lysates.

Together, these data confirm the successful isolation and differentiation, using PDGF BB, of smooth muscle phenotype cells from progenitors in human blood. Our results indicate that SPCs exist in adult human blood and raise the possibility that PDGF BB in the bone marrow, in the blood stream or at the vessel wall/endothelial interface may facilitate smooth muscle cell differentiation from vascular progenitors at these sites.

GENETICS IN ATHEROSCLEROSIS

P2821 Angiotensinogen gene T235 variant: risk of coronary artery disease and myocardial infarction in a German population

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The thymidine to cytosine transition at postion 704 in exon 2 of the angiotensinogen (Ao) gene, which results in an amino acid substitution of threonine for methionine at the protein level, is associated with elevated Ao plasma concentrations. The data on this mutation and an association with coronary artery disease (CAD) are inconclusive. Therefore the aim of this study was to investigate the role of this polymorphism in a large population who underwent coronary angiography at our institution.

Methods: A total of 1282 individuals who underwent coronary angiography were genotyped. In 836 subjects (65.2%) CAD was present. The remaining 446 (34.8%) – with excluded CAD – served as controls. In the entire population the genotype frequencies were 30.3, 51.6 and 18.1% for the AA, Aa and aa genotype, respectively (A=wildtype allele, a=mutant allele). The results are summarised in the Table.

Results:

	AA	Aa	aa	P
Age (yrs)	60.7 (10.5)	60.4 (9.5)	59.9 (9.4)	n.s.
BMI (kg/m^2)	27.1 (3.8)	26.8 (3.5)	27.4 (3.6)	n.s.
LDL-C	4.23 (1.23)	4.17 (1.22)	4.29 (1.19)	n.s.
Smoking (pyrs)	12.7 (18.2)	12.2 (17.0)	12.1 (17.3)	n.s.
Sex (%male)	67.6	72.5	72.8	n.s.
Diabetes (%)	25.5	23.1	22.0	n.s.
Hypertension (%)	57.1	59.5	64.7	n.s.
CAD (%)	64.8	64.8	61.2	n.s.

Date are given as mean (SD) or as %. Comparison by ANOVA with Bonferroni correction or chi-square testing.

The multivariate analysis showed that neither the A nor the a allele carries an independent risk for the development of CAD. In contrast, CAD patients who carry the A allele had a significantly increased risk for myocardial infarction, OR=1.5 (95% CI 1.003-2.25).

Conclusion: In conclusion, our data indicate that the Ao T235 variant is not an independent risk factor for CAD. The A allele however, is in CAD patients significantly associated with myocardial infarction.

P2822 Identification of autosomal dominant heritability of myocardial infarction

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Myocardial infarction (MI) is considered to be a multifactorial disease that results from an integrated vascular response to common cardiovascular risk factors. Interestingly, some families show a high incidence of MI that cannot be explained by these traditional risk factors. Thus, the aim of this study was to investigate whether MI can be also inherited in a Mendelian pattern.

Methods: In cooperation with 17 in-hospital cardiac rehabilitation centers, the Regensburg MI family study group screened over 200.000 medical reports of MI patients in order identify extended MI families.

Results: We identified 124 MI families with at least 3 or more affected living MI siblings. In 18 of these families without bilinearity, 101 living MI patients and 375 unaffected family members were recruited. Moreover, 43 patients had died from MI in these families. The largest MI family had 64 family members and 22 affected individuals in five generations. In the age group from 50 to 70 years, on average 50% of the family members were affected and nearly 100% of MI patients had parents carrying the disease. Traditional cardiovascular risk factors, such as smoking, hypercholesterolaemia, hypertension and diabetes mellitus, had the same frequencies as a population-based sample of sporadic MI (KORA-Augsburg, Germany, n=609, $p>0.1$ for all risk factors). However, the predominance of male gender as usually seen in MI registries was less pronounced in MI families (71.5% vs. 87.4%, in the population based KORA MI registry, $p<0.001$). Furthermore, the patterns of inheritance argued against imprinting or a X-chromosomal disorder. In the MI families, power simulation using the SLINK software package and applying several models of potential inheritance revealed consistently the highest theoretical LOD scores under the assumption of an autosomal dominant heritability. A maximal simulated LOD score of 3.0 was obtained in a single large family using the affected only model. After age-adjusted consideration of the non-affected individuals, the maximal simulated LOD score increased to 6.2 and was significant in four of the 18 families.

Conclusion: A minority of MI patients shows an autosomal dominant heritability which cannot be explained with traditional cardiovascular risk factors. The data suggest novel genetic mechanisms resulting in myocardial infarction.

P2823 Dissection of individual contributions of apolipoprotein (a)-gene-polymorphisms to the risk of myocardial infarction

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Genetic polymorphisms at the LPA-locus on chromosome 6 determine a large part of the variablity of serum concentrations of lipoprotein(a) [Lp(a)]. The size of Lp(a) particles is variable as well, being largely determined by the kringle IV repeat (KIVR) polymorphism of this gene. The impact of interactions of this polymorphism with polymorphisms of the promoter region (pentanucleotide repeat, PNR) on atherogenicity of Lp(a) particles and cardiovascular risk is not understood.

We determined the association the KIVR polymorphism and the PNR repeat polymorphism with serum Lp(a) levels and myocardial infarction in 786 age and gender matched MI-patients and controls from the general population (50% women). Elevated Lp(a) serum concentrations were associated with increased MI-risk (odds ratio 1.81 in men and 2.52 in women for Lp(a) in the upper quartile; $p<0.0001$). The KIVR polymorphism determined 50% of total Lp(a) variability. However, despite the overall large effect of the KIVR polymorphism on Lp(a) concentration the association with MI was relatively weak. In contrast, the promoter PNR polymorphism which explains only 6% of the total variabilty of Lp(a) was significantly associated with MI in women (adjusted rel. risk for homozygous carriers of 8 PNR 1.39, $p<0.023$). We, therefore, investigated whether interactions of the two polymorphisms may be of relevance. Specifically, we hypothesized that a large number of small Lp(a) particles may be detrimental. Interestingly, in carriers of <25 KIVR the variation of Lp(a) concentrations was very large (median 29.5 mg/dl, interquartile range 68.2). By contrast, in the presence of >25 KIVR this variability was low (median 8.3, interquartile range 17.7 mg/dl). Moreover, we observed a strong linkage disequilibrium between the KVIR and the PNR polymorphism. In particular, 10,11 and 12 PNR are almost exclusively present in individuals that carry <25 KIVR and, thus, express small Lp(a) particles. In these individuals, the PNR polymorphism is the major modulator of Lp(a) concentration [median of Lp(a) in homozygous carriers of 8 PNR 72.6 mg/dl vs. 14.6 mg/dl in 10, 11, 12 PNR; $p<0.0001$].

Polymorphisms of the apolipoprotein(a) gene (KVIR and PNR) modulate both size and number of Lp(a) molecules. Linkage disequilibrium between the KIVR and the PNR polymorphism explains a strong influence of the PNR polymorphism on Lp(a) concentration in individuals expressing small Lp(a) molecules. These individuals may be at particularly high risk, if they carry 8 PNR.

P2824 The methylenetetrahydrofolate reductase polymorphism gene is associated with increased DNA damage in coronary artery disease

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Background: Somatic DNA damage has been associated to the pathogenesis of atherosclerosis. Recently, it has been also observed that elevated levels of plasma homocysteine (Hcy) can induce DNA damage.

Aim: In this study we investigated whether DNA damage is related to the C677T variant in the methylenetetrahydrofolate (MTHFR) gene as well as to plasma levels of Hcy, B12 and folate in patients with coronary artery disease (CAD).

Methods and Results: Patients (n=46) with angiographically-proven CAD were studied by using micronucleus (MN) test, an accepted method for evaluating genetic instability. TT patients had plasma Hcy levels higher than those with the CT or CC genotypes (27.8±5.2 vs 13.7±2.2 and 12.9±1.9 μmol/L, respectively; p=0.004). Patients with multi-vessel disease had higher plasma Hcy levels (11.6±1.2, 22.0±4.7, 19.3±3.9 μmol/L for one-, two- and three-vessel disease, respectively; p=0.05). The MN index increased with the number of affected vessels (8.4±0.7, 11.1±2.0, 14.2±1.7 for one-, two-, and three-vessels disease, respectively; p=0.02) and was significantly higher in subjects with TT genotype compared with the CC or CT genotypes (15.7±2.4 vs 8.9±1.7 and 9.9±0.8, p=0.017 and p=0.025, respectively). The MN index was also negatively correlated with plasma B12 concentration (r= -.343, p=0.019) and positively with plasma Hcy (r=.429, p=0.005).

Conclusions: These data indicate that increased somatic DNA damage is related to MTHFR polymorphism and elevated levels of Hcy, suggesting an interesting link between coronary atherosclerosis and genetic instability in humans.

P2825 The IL6/G-174C polymorphism modulates the impact of pathogen burden on coronary artery disease

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Background: The number of infectious pathogens to which an individual has been exposed (pathogen burden) has been linked to the development and the prognosis of coronary artery disease (CAD). The interaction between infection, genetic host susceptibility and CAD remains unclear.

Objectives: This study was aimed at evaluating the association between CAD and pathogen burden. Modulation of the association by serum levels of inflammatory markers and polymorphisms of the interleukin-6 (IL-6) and tumor necrosis factor (TNF)-alpha genes was also investigated.

Methods: IgG or IgA antibodies to 8 pathogens were determined in 991 CAD patients and 333 control subjects. Serum levels of high sensitive C-reactive protein, fibrinogen, IL-6, TNF-alpha were also measured. All subjects were genotyped for the IL6/G-174C, the TNF/C-851T and the TNF/G-308A polymorphisms.

Results: Single pathogens (C pneumoniae, CMV, H pylori and HSV-1) were positively related to the presence of CAD. A strong association between increasing pathogen burden and CAD was confirmed. The prevalence of a high pathogen burden (>=4 pathogens) was 50.4% in cases and 21.2% in controls ($p<0.0001$). A high pathogen burden was associated with decreased HDL-cholesterol levels both in cases and controls ($p<0.001$). The association between CAD and pathogen burden was modulated by the IL6/G-174C polymorphism, the odds ratio (OR) being higher in GC heterozygotes (OR 3.45, 95% CI 1.99-5.98) than in both types of homozygotes (OR 1.31, 95%CI 1.69-2.50 in GG homozygotes, OR 1.58, 95%CI 0.64-3.91 in CC homozygotes; $p<0.05$ for interaction). This interaction appeared to be mediated by variations in serum IL-6 levels.

Conclusions: Pathogen burden is strongly associated with the risk of CAD. This effect might be partly mediated by a decrease in HDL-cholesterol levels. The IL6/G-174C polymorphism appears to act as a modulator of the effect of pathogen burden on CAD risk, through variations in circulating IL-6 levels, and possibly local production of IL-6.

P2826 Gene-environment interaction in coronary artery disease: protective effect of eNOS-Glu-298-Asp-polymorphism in non-smokers, but not in smokers

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Background: Asp-homozygosity of the eNOS Glu298Asp polymorphism has been previously associated with elevated risk of coronary artery disease (CAD) or myocardial infarction (MI).
Objective: Impact of eNOS Glu298Asp-polymorphism on prevalence of CAD and MI in relation to smoking habits in consecutive patients scheduled for coronary angiography.
Methods: Analysis of participants of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, which comprises a coronary angiography and thorough evaluation of cardiovascular risk factors. Analyis of eNOS genotype by restriction analysis.
Results: Multivariate odds ratios (95%-CI) adjusted for age, gender, and concomitant cardiovascular risk factors:
Multivariate odds-ratio for CAD: Smoker 1.14(0.84-1.54), n=955; Non smoker 0.89 (0.63-1.25)n=689
Multivariate odds-ratio for MI: Smoker 1.06 (0.76-1.49), n=618; Non smoker 0.48 (0.28-0.82)n=333
Conclusion: In non-smoking subjects with stable CAD the eNOS Glu298Asp polymorphism is associated with lower prevalence of MI. This protective effect has been not observed in smoking subjects.

P2827 Stromelysin-1 gene promotor 5A/6A polymorphism and C-reactive protein in patients with coronary artery disease

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The purpose of this study was to compare the 5A/6A polymorphism of the stromelysin-1 gene promoter between patients with coronary artery disease (CAD) and healthy control subjects, and to explore the relation of 5A/6A genotypes with high sensitivity C-reactive protein (CRP).
This study included 336 Chinese patients with CAD diagnosed by coronary angiogram of at least 50% stenosis in vessels and 389 matched healthy controls. High sensitivity CRP levels were measured in fasting plasma samples. Stromelysin-1 5A/6A genotypes were determined by the polymerase chain reaction and restriction enzyme analysis.
The CAD patients showed significantly higher 5A/5A genotype percentage (18.3% vs. 7.7%, $p < 0.001$) and greater 5A-allele frequency (0.335 vs. 0.279, $p < 0.05$) than healthy control subjects. High sensitivity plasma CRP levels were also significantly elevated in CAD patients than in controls (2.62 ± 3.53 vs. 0.86 ± 1.01 mg/L, $p < 0.001$). Patients with 5G/5G genotype had significantly higher plasma CRP (3.93 ± 4.72 vs. 2.81 ± 3.01 and 1.94 ± 2.42 mg/L, $p < 0.05$) than those with 5A/6A and 6A/6A genotypes.
The study showed that the 5A/5A genotype of the stromelysin-1 gene promoter was associated with higher risk for CAD and increased CRP level in a Chinese population. It suggested that the 5A/5A stromelysin-1 gene variant could be a genetic risk factor associated with atherothrombosis and inflammation.

P2828 Premature coronary artery disease shows no evidence of linkage to locus encoding for human alpha oestrogen receptor

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An association between a dinucleotide repeat polymorphism in the upstream region of the human alpha oestrogen receptor gene with premature coronary artery disease has been reported (BMJ 2000;321:273-4). We examined the relevant locus using a linkage approach.
Sibling pairs recruited as part of the BHF Family Heart Study and affected with premature coronary artery disease (Myocardial Infarction, Coronary Artery Bypass Grafting, Percutaneous Coronary Intervention or definite Angina before the age of 65) were examined. DNA was extracted from whole blood by a standard method. The region of interest was amplified by polymerase chain reaction using the same pair of markers that was used in the initial study that reported the association. Products were analysed by capillary gel electrophoresis. Single-point linkage analysis based on the likelihood ratio test was performed using SPLINK software.
416 families were genotyped consisting of 382 sibling pairs, 29 trios and 5 sets of 4 siblings. No significant linkage was observed in the whole cohort (equivalent LOD score 0.14, p=0.27) or in the pre-specified subgroups of male sib pairs (n=287 independent sib pair comparisons, LOD= 0.18, p= 0.23) or sibs with acute myocardial infarction (n= 173 sib pairs, LOD= 0.02, p= 0.58).
We were unable to detect linkage to the locus encoding for the oestrogen receptor. Population differences, differences between genetic predisposition towards fatal versus non-fatal coronary disease and statistical problems (spurious associations, power) may explain differences between studies.

P2829 Deletion polymorphism of the angiotensin I-converting enzyme gene is a potent risk factor for coronary artery ectasia

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Background: Coronary artery ectasia (CAE) is characterized by irregular, diffuse, saccular, or fusiform dilatation of the coronary arteries. The mechanism(s) involved in the genesis of CAE are not fully understood. In this study we sought to assess the role of insertion/deletion (ID) polymorphism of angiotensin converting enzyme (ACE) gene,in the development of CAE.
Methods and Results: We prospectively evaluated 3427 consecutive patients who underwent coronary angiography for diagnostic purposes and found that 152 (4.4%) had CAE. Of the 152 patients, 108 (71%) had coexisting significant coronary artery disease (>50% diameter stenosis in any of the major epicardial arteries), whereas 44 (29%) had either no or nonsignificant coronary artery stenosis. Clinical examinations and laboratory investigations revealed no evidence of a collagenosis, connective tissue or inflammatory disease as an underlying etiology. Of the 152 ectatic patients, 82 (53.9%)had the DD genotype, 49 (32.3%) had the ID genotype and 21(13.8%) had the II genotype. Control group consisted of 158 age and sex matched patients with significant coronary artery disease but without any evidence of ectasia. No significant differences were noted between the two groups when features such as hypertension, diabetes, hypercholesterolemia, family history of coronary artery disease, cigarette consumption, incidence of prior myocardial infarction, and left ventricular ejection fraction were examined. The ACE genotype frequencies were significantly different between the two groups, DD genotype beeing more prevalent among patients with CAE (p= 0.0046). Multivariate analysis demonstrated the ACE DD genotype as the only significant risk factor for CAE development in this population. The adjusted odds ratios were 2.16 (95% CI 1.34-3.41, p=0.0027) for DD patients versus II/ID patients and 2.16 (95% CI 1.12-4.14, p=0.02) for DD patients versus II patients.
Conclusion: The ACE DD genotype seems to be a potent risk factor for the development of CAE. The implications of our findings and the underlying mechanisms need to be fully assessed and investigated.

STEM CELLS: METHODOLOGY

P2830 VEGF did not improve left ventricular function after transplantation of fetal cardiomyocytes after myocardial infarction in the rat

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Objectives: Recent studies have demonstrated feasibility of transplanting fetal cardiomyocytes after myocardial infarction (MI) with improvement of LV-function. The mechanism of improvement is not understood yet due to release of angiogenetic factors by fetal cells in ischemic myocardium-
Methods: Male ventricular fetal cardiomyocytes were injected into marginal regions of MI, 4 weeks after suture occlusion of the left coronary artery in adult female rats with and without VEGF. Sham-operated hearts received VEGF with IMDM or without VEGF. Two months after transplantation(Tx), engrafted cells were traced by fluorescence-in-situ-hybridization (FISH) for Y-chromosomes, LV-dimensions and function was assessed by 2-D and 3-D echocardiography. LV-pressure and coronary flow was measured ex vivo in a Langendorff-perfusion-system and capillary density by factorVIII-staining (n=12 each).
Results: FISH revealed presence of transplanted cells in infarcted host myocardium in association with neovascularization with and without VEGF. Enddiastolic LV-diameter and LV-volumes (3-D-echocardiography) slightly increased in sham-operated rats with and without VEGF, but markedly decreased after Tx with and without VEGF-application (not $p<0.001$ compared to sham-operated). Conversely, fractional shortening declined in sham-operated rats with and without VEGF ($p<0.005$), however gradually increased after Tx with and without VEGF ($p<0.005$).
Conclusions: Transplanted cardiomyocytes-rich graft cells persist in host myocardium and mediate continuous improvement of LV-function and survival in rat model of MI without effect of VEGF-co-transplantation.

P2831 In vitro stimulation of murine pluripotent P19 stem cells by dimethylsulfoxide using the embryoid body-method

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Background: In various studies DMSO has been described as a differentiation factor for P19 cells (mouse teratocarcinoma cells); one of the differentiated cell types induced by DMSO are cardiomyocytes. In this study differentiation was accomplished by cultivating P19 cells into embryoid bodies, in which the cells have contact with nothing else than the cells in the embryoid body.
Methods: The effects of 1% DMSO on differentiation response of P19 cells were studied after incubation in hanging drops (volume of each drop 20 il) containing cultivation medium (DMEM) supplemented with 20% FBS, 1% DMSO and approximately 400 cells each for 3 days. Cell aggregates, further referred to as embryoid bodies, were transferred from the hanging drops into 24-wells tissue culture plates (1 embryoid body/well) containing normal cultivation medium (DMEM + 10% FBS + 1% Penicilline/Streptomycine + 1% Amino acids), in which the embryoid bodies attached to the bottom and cells started to grow out.
To prove that P19 cells actually differentiated into cardiomyocytes, heart-specific proteins (such as á-actinin) in the differentiated cells were demonstrated using immunofluorescent microscopy. Next to this technique, the embryoid bodies were observed daily, using a microscope, to detect spontaneous contractions.
Results: On day 13 (3 days in hanging drops (DMSO+) and 10 days in the 24-well tissue culture plates (DMSO-)), spontaneously beating cells and cellgroups were observed. With the use of immunofluorescent microscopy, fluorescent cell groups were observed, which indicate the presence of á-actinin in the cells.
Conclusion: The observation of spontaneously beating cells and á-actinin positive cells showed differentiation of the pluripotent P19 stem cells into cardiomyocytes.

P2832 Monocyte transplantation – New tool for in vivo augmentation of collateral vessel growth

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Therapeutic augmentation of collateral vessel growth (arteriogenesis) is of tremendous interest for alleviation of morbidity and mortality from ischemic deseases. Monocytes/macrophages (Mo) represent key players of arteriogenesis. They home to sites of hemodynamically relevant stenoses thereby locally creating a highly arteriogenic environment through secretion of growth factors and cytokines. We thought to exploit Mo homing for augmentation of arteriogenesis via ex vivo engineering and injection into rabbits after ligation of their right femoral artery. Monocytes were isolated from rabbit blood by modified Ficoll-Paque gradient centrifugation and plated in medium supplemented with 200 U/ml granulocyte macrophage-colony stimulating factor (GM-CSF) for 24 h. Different amounts of GM-CSF-activated Mo were then intravenousy injected into rabbits 24 h after ligation. 7 days later maximal adenosine-induced conductance (C= flow/mean arterial pressure - mean peripheral pressure, ml/min/100 mmHg) was determined using an ultrasonic flow probe placed around the right external iliac artery. Injection of 3x107 Mo resulted in a 22% rise of C from 105±5 to 128±5 (n= 5, $p<0.05$). Increasing their number to 1.5x108 led to a further augmentation of C to 202±11 (+92%, $p<0.05$) beeing close to values determined in unligated control vessels (262±10, each n=5). Angiographic evaluation of the right thigh demonstrated a significant increase of collateral vessels (no ligation: 5±1; ligation: 11±2, ligation + 3x107 Mo: 16±2; ligation + 1.5x108 Mo: 21±2). The homing of injected Mo was demonstrated by their ex vivo viral infection with the reporter LacZ and later histologic visualization close to collateral vessels. GM-CSF plays an imortant role in arteriogenesis. We, therefore, infected 3x107 Mo with an adenoviral vector coding for GM-CSF (25 pfu) 24 h prior to injection. C was determined 69% elevated (178±8) at day 7 compared with control-infected Mo (122±7, n=5, $p<0.05$). Mo represent an intriguing tool to augment arteriogenesis. Ex vivo activation is able to increase their arteriogenic properties. Furthermore, they can additionally serve as vehicles for genetherapeutic approaches.

P2833 Atorvastatin inhibits the senescence of human endothelial progenitor cells

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Endothelial progenitor cells (EPC) play an important role in postnatal neovascularisation of ischemic tissue. Ex vivo expansion of EPCs might be useful for potential cell therapy of myocardial ischemia. However, cultivation of EPCs leads to cellular aging (senescence) which is associated with a reduced proliferative capacity. Therefore, we investigated whether statins might be able to prevent senescence of EPCs.
Results: EPCs were isolated out of peripheral blood and cultivated in EBM medium (medium and supplementary growth factors, Cell Systems) and 20% FCS. FACS analysis revealed that more than 80% of adherent cells stained positive for the endothelial marker proteins KDR, eNOS and VE-cadherin. However, already 2 days after cultivation, EPCs become senescent as determined by acidic β-galactosidase staining (day 2: 88 ± 6.6%, day 4: 100 ± 0.6% senescent cells). Atorvastatin (AT) dose-dependently (1nM-1μM) inhibits the onset of EPC senescence in culture (day 2: 38 ± 12% p=0.01; day 4: 11 ± 4%, $p<0.001$). Similar results were obtained with mevastatin, which demonstrates a class effect of statins. Moreover, AT increased the proliferation of EPCs as assessed by BrdU proliferation assay. Consistent with the increase in proliferation, the cell cycle regulator cyclin F was upregulated in AT-treated EPCs.
To gain further insight into the mechanism of the senescence inhibitory effects of statins, we investigated the role of NO. However, inhibition of the NO-synthase (LNMMA, 1mM) did not reverse the effect of AT. Likewise, exogenous NO (SNAP, 20μM) did not prevent the onset of senescence. Because inhibition of the HMG-CoA reductase also reduces the formation of the products geranylgeranyl- and farnesylpyrophosphate (GGPP and FPP) and, thereby, abolishes Rho-kinase activation, we determined the effect of the above named substrates and the Rho-kinase inhibitor HA1077 (10μM). GGPP and FPP (10μM) reversed the effect of AT (day 4: 77 ± 6.6%, $p<0.001$ and 61 ± 8%, $p<0.001$ senescent cells, respectively), whereas inhibition of the Rho-kinase alone could not prevent the onset of senescence (day 4: 91 ± 3% senescent cells).
Conclusions: Atorvastatin inhibits the senescence of EPCs independent of NO and Rho kinase but dependent on GGPP and FPP. AT-mediated prevention of EPC senescence might be due to a regulation of cell cycle proteins. The inhibition of EPC senescence and improvement of EPC proliferation by statins in vitro may importantly contribute to improve functional activity of EPCs for potential cell therapy.

CONTRACTILE FUNCTION

P2834 Adrenomedullin: calcium dependent inotropic effects in isolated human myocardium

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Adrenomedullin (ADM) is a recently discovered endogenous peptide with potent vasodilatory effects. In heart failure, plasma levels of ADM are elevated, but it is unknown whether ADM directly affects cardiac contractile functions. We tested functional responses to ADM in human atrial and ventricular myocardium.
Methods: Isolated atrial (n=11), ventricular non-failing (n=10) and ventricular failing (n=18) trabeculae were electrically driven at 1 Hz, 37°C. Application of ADM 0.1 μmol/l or 1 μmol/l and simultaneous registration of contractile force and calcium transients (Aequorin light signal (AL)). Application of Isoproterenol (0.003 μmol/l) or $[Ca^{2+}]_o$ 3.2 mmol/l for comparison.
Results: ADM significantly increased contractile force in atrial myocardium (by maximally 33 ± 6% at 1 μmol/l; $p<0.05$) with an overproportional increase in AL (by 69 ± 15%, $p<0.05$). In non-failing ventricular muscles force increased by 8 ± 2% ($p<0.05$; AL not done). In failing ventricular muscles the inotropic effect was marginal (increase by 5 ± 1%; $p<0.05$), but also associated with an overproportional increase in AL (by 18 ± 5%; $p<0.05$; dF/dL= 0.3 ± 0.2). Isoproterenol (equiactive concentration: 0.003 μmol/l) increased force in ventricular muscles by 5 ± 2% and AS by 15 ± 5% ($p<0.05$; dF/dL = 0.3 ± 0.1) whereas $[Ca^{2+}]_o$ (3.2 mmol/l) resulted in proportional changes (force increased by 25 ± 3%, AL by 24 ± 5%; dF/dL = 1.0 ± 0.1). As with Isoproterenol ADM slightly decreased relaxation times.
Conclusions: ADM exerts marked positive inotropic effects in atrial and slight inotropic effects in ventricular myocardium. These effects are associated with overproportional increases in intracellular calcium transients. We suggest a potential cAMP-dependent mechanism of action of ADM in human cardiac muscle.

P2835 Mutation of the calcineurin binding site in FKBP12.6 leads to loss of the FKBP12.6 mediated increase in contractile performance

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In heart failure, Ca^{2+} release from sarcoplasmic reticulum (SR) is impaired. The 12.6 kDa FK-506 binding protein (FKBP12.6) binds to and modulates the cardiac SR calcium release channel (ryanodine receptor, RyR2) and plays an important role in the pathogenesis of heart failure. We have recently shown that overexpression of FKBP12.6 in cardiomyocytes reduces spontaneous Ca^{2+} leak and increases contractility. Despite binding to RyR2, FKBP12.6 also binds to the Ca^{2+}-dependent protein phosphatase Calcineurin (CAN), but it is not clear whether CAN plays a role in the FKBP12.6 mediated regulation of RyR.
We have constructed a mutant form of FKBP12.6 (FKBP12.6M), which is unable to bind CAN, by exchange of two amino acids (G89P, V90K). Lack of CAN binding was demonstrated in a CAN phosphatase assay using recombinant FKBP12.6M. In this assay, absence of FK506 mediated CAN inhibition by FKBP12.6M was observed and rotamase assays showed preserved binding of FK-506 to FKBP12.6M. We used adenovirus mediated gene transfer for overexpression of FKBP12.6M in isolated rabbit cardiomyocytes. RT-PCR showed the presence of FKBP12.6M RNA and antiserum, raised against the mutated region of FKBP12.6M, confirmed overexpression of FKBP12.6M in western blots.
While overexpression of FKBP12.6 increases contractility, FKBP12.6M did not enhance relative shortening (RS) at a multiplicity of infection (MOI) of 10 when compared to beta-galactosidase control transfected myocytes (2,7±0,1% RS n=117 vs 2,8±0,1% RS n=120, p=0,528). At MOI 50, RS was even significantly diminished (3,9±0,2% RS n=121 vs. 4,4±0,2% RS n=117, p=0,02). Thus, the positive inotropic effect of FKBP12.6 requires an intact Calcineurin binding site. This points to an important role of Calcineurin in the regulation of myocardial contractility.

P2836 Adenoviral overexpression of the Na^+/Ca^{2+}-exchanger in adult rat cardiomyocytes reduces contractile performance and Ca^{2+}-transient

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The influence of the Na^+/Ca^{2+}-exchanger (NCX) on the Ca^{2+}-homeostasis of the cardiomyocytes and its functional relevance during the contraction cycle is discussed very controversially. The present study aimed to study the effect of the NCX in a NCX-overexpressing model; i.e. isolated rat cardiomyocytes with adenovirus mediated (Ad5NCX/GFP) NCX-overexpression. To reveal dominant changes via the transgene NCX-overexpression, the rat was chosen as a model with a small physiological influence of the NCX on Ca^{2+} handling.
Protein expression was studied by Westernblot analysis with specific antibodies; NCX activity was analyzed with Na^+-dependent 45Ca-uptake. Functional studies were performed with a video edge detection system and after stimulation of cells with increasing frequency, Ca^{2+}, and CPA (Cyclopiazonic Acid, inhibitor of SERCA 2a) in isolated myocytes. Cardiomyocytes infected with Ad5GFP served as the control group.
Westernblot analysis showed a significant increase of the NCX (more than five fold DU) 48h after transfection (10 MOI) whereas other calcium-modulating proteins (SERCA 2a, PLB, Calsequestrin) were unchanged. NCX specific 45Ca-uptake was increased threefold.
In NCX-cells basal and Ca^{2+}-stimulated contractile performance and Ca^{2+}-transients (FURA 2a) were diminished with a more negative force-frequency behavior ($p<0,05$). Inhibition of SERCA 2a by CPA resulted in a significant better diastolic relaxation in NCX-cells compared to control.
Thus, NCX-overexpression might result in depletion of systolic intracellular Ca^{2+}-availability due to activation of Ca^{2+}-extrusion during diastole. Diastolic Ca^{2+}-extrusion by the NCX is especially supported in a condition with reduced SERCA 2a activity.

P2837 Atorvastatin impairs contractile function in engineered heart tissue

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It is not known whether HMG-CoA reductase inhibitor therapy interferes with cardiac myocyte contractile function. We examined the effects of atorvastatin (ATOR) on isometric force of contraction (FOC) and contraction kinetics in engineered heart tissue (EHT). Myocytes isolated from neonatal rat hearts were reconstituted in a collagen matrix. Resulting EHTs were cultivated for 6 d before treatment with ATOR (1 μM) for additional 5 d. Thereafter, EHTs were placed into organ baths and FOC, time of contraction (T1) and time of relaxation (T2) were recorded under electrical stimulation. Basal FOC was not altered by ATOR compared to vehicle treated controls. However, the response to cumulative concentrations of Ca^{2+} (increase in FOC over basal 0.41±0.03 vs. 0.52±0.03 mN, n=26) and isoprenaline (0.21±0.01 vs. 0.30±0.02 mN, n=26) was significantly diminished. In addition, T1 (ISO 1nM: 43±1 ms vs. 40±1 ms, n=26) was significantly prolonged whereas T2 was not changed. Co-administration of mevalonic acid (MA, 200 μM) completely reversed the effects of ATOR. MA alone had no significant effects. 14C-Phenylalanine incorporation assays revealed that ATOR diminished protein synthesis in EHTs by 17% ($p<0.05$). Interestingly, ATOR significantly reduced the naturally occurring loss of cells in EHTs during cultivation. Immunofluorescence staining of sarcomeric actinin showed no obvious differences in cardiomyocyte morphology and sarcomere organization. The current findings for the first time demonstrate impaired contractile response after ATOR treatment in reconstituted heart tissue. This occurs despite a general cytoprotective effect of ATOR as suggested by increased cell count. This study sheds a new light on HMG-CoA reductase inhibitor actions besides the well established beneficial effects on atherogenesis and endothelial function.

STRESS ECHOCARDIOGRAPHY

P2838 Noninvasive assessment of left anterior descending artery coronary flow reserve by transthoracic echocardiography: feasibility and results

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Background: Coronary flow reserve (CFR) is a key physiological parameter which can be evaluated noninvasively by transthoracic echocardiography (TTE) during vasodilator stress. Aim: To assess the feasibility and physiologic meaning of TTE assessment of CFR. Methods: Starting June 1, 2000 to August 1, 2001, 239 consecutive patients (147 males; age=67±19 years) were referred for stress echocardiography. In all, TTE (S12-S8 probe, HP 5500, Agilent technology) evaluation of distal left anterior descending (LAD) coronary artery was attempted at baseline and following dipyridamole (0.84 mg/kg). Wherever color-coded LAD blood flow from the baseline could not be obtained, contrast enhancement with Levovist (Schering AG) was used. Peak diastolic coronary flow velocity of LAD was recorded by pulsed Doppler under the guidance of Color Doppler flow mapping. CFR was calculated as the ratio of dipyridamole/rest peak diastolic flow velocity. Results: The overall feasibility was 93% in the first 100 patients and rose to 98% in the latter 139 ($p<.05$). The need for contrast injection was 38% in the first 100 and 18% in the latter 139 patients ($p<.01$). In patients with complete clinical and angiographic characterization, CFR values were 3.2±0.3 in control group (n=14); 2.4 ± 0.4 in Syndrome X (n= 43); 2.5±0.3 in patients evaluated early after CABG with left internal mammary artery on LAD (n=28); 2.3 ± 0.4 in patients evaluated early after PTCA (n=45); 1.4±0.2 in critical (>70%) native LAD stenosis (n=24); 1.85±0.22 in dilated cardiomyopathy (n=8); 2.01±0.2 in hypertrophic cardiomyopathy (n=9); 1.8±0.3 in aortic stenosis (n= 7). Conclusion: Noninvasive evaluation of CFR by TTE is highly feasible in the echo lab during vasodilator stress echo. After a limited learning curve, contrast injection is rarely needed - further simplifying and reducing the cost of examination. Physiologically congruent results of potential clinical value can be obtained during vasodilator stress echo in different pathophysiological conditions, ranging from coronary artery disease to cardiomyopathy.

P2839 Stress-echo, coronary flow reserve and color tissue Doppler after coronary angioplasty in patients with previous anterior myocardial infarction

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Aim of the study was to identify possible associations between coronary flow reserve (CFR) and myocardial functional indexes measured by color Tissue Doppler (cTD) after secondary percutaneous transluminal coronary angioplasty (PTCA) in patients with previous anterior myocardial infarction (MI).
Methods: Twenty men (age = 55 ± 5 years) affected by previous anterior MI, 3-6 months after secondary PTCA of left anterior descending coronary artery (LAD), underwent: noninvasive CFR estimation in distal LAD (ratio between hyperemic and basal coronary diastolic flow velocities) by high-frequency Doppler-echo; dobutamine (Dob) stress-echocardiography with determination of wall motion score index (WMSI) on 16 segments and normal myocardium percentage (number of segments with score = 1/16 segments × 100); cTD of middle posterior septum with quantitative analysis of myocardial systolic (Sm) and diastolic (Em and Am) peak velocities, both at baseline and at high Dob dose. According to CFR, patients were divided into 2 groups: 10 with CFR considered as normal according to the reference values of intracoronary Doppler flow wire after MI (> 1.6) and 10 with reduced CFR (< 1.6).
Results: The 2 groups were comparable for age, blood pressure, heart rate, left ventricular (LV) ejection fraction and WMSI at rest. Patients with impaired CFR showed an increase of WMSI and a reduction of normal myocardium percentage at high-dose Dob (both $p<0.01$) in comparison to the group with normal CFR. cTD displayed comparable septal Em/Am ratio both at rest and at high-Dob but Sm, similar between the 2 groups at rest, was lower in patients with CFR < 1.6 at low-Dob ($p<0.05$) as at high-Dob ($p<0.01$). In the overall MI population, CFR had negative relation with high-Dob WMSI ($r = -0.54$, $p<0.01$) and positive association with high-Dob septal Sm ($r = 0.66$, $p<0.001$). This last relation remained significant even after adjusting for diastolic blood pressure, heart rate and high-Dob WMSI (standardized β coefficient = 0.56, $p<0.01$).
Conclusions: The function of coronary microvessel circulation predicts the recovery of myocardial reserve in LV segments corresponding to the coronary artery (= LAD territory) involved into the re-perfusion procedure after MI. The combined use of Doppler-echo derived CFR and cTD applied to stress-echo is promising for evaluating the successful results of secondary PTCA.

P2840 Prognostic significance of grafted left internal mammary artery flow reserve estimated by noninvasive dobutamine Doppler

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In pts post CABG with LIMA grafted to LAD, interrogation of underlying ischemia in LIMA/LAD territory may be performed using LIMA flow reserve (CFR) by noninvasive Doppler using either adenosine or dobutamine. We assessed the relative contribution of LIMA/LAD CFR by dobutamine (CFRdob) for prediction of cardiac events (CE) compared to the respective SPECT Tl201 and dobutamine stress echo (Dob-echo) outcome.
Methods: 52 consecutive pts (age 66±9) were studied within a range of 1-15 years (6±4) post CABG. LIMA CFR was estimated (proximal LIMA:supraclavicular fossa) during the dobutamine 30μg/kg/min stage of Dob-echo protocol. All pts underwent coronary angiography and SPECT Tl201 within a period <3months. The cut off point of 1.27 for CFRdob was predictor of LIMA/LAD patency, derived from receiver operating curve analysis (area: 0.79, p: 0.002, sens: 0.71, spec: 0.90)
Results: 12 pts had a significant stenosis (>70% diameter) either in the LIMA or in LAD distal to the anastomosis. During a follow up period of 18±11 months, 11 pts had CE(death, myocardial infarction, angina, revascularization). Pts had a telephone interview and coronary risk profile/treatment were obtained from chart review.
Pts with or without CE had similar age (66±7 vs 62±9), time elapsed from CABG (years:7±4 vs 6±3), EF (%:44±10 vs 49±8) and follow up (months: 18±10 vs 18±11). The two groups had similar incidence of CAD risk factors and use of B-blockers, CEI, statins during follow up. In stepwise logistic regrsession analysis (SLRA) for prediction of CE including SPECT outcome for LAD territory and CFRdob, then CFRdob had an independent contribution ($R=-0.32$, $p=0.03$ with $exp(b)=0.09$, thus implying a 11 odds ratio for CE when CFRdob<1.3). When Dob-echo outcome for LIMA/LAD ischemia was included with CFRdob in SLRA, then CFRdob had an independent contribution ($R=-0.36$, $p=0.03$ with $exp(b)=0.05$, thus implying a 20 odds ratio for CE when CFRdob<1.3). When EF was considered, the contribution of CFRdob remained unchanged ($R=-0.21$, $p=0.06$, $exp(b)=0.13$, odds ratio=7.7). Consideration in SLRA of two different models, one including CAD risk factors and the other the use of b-blockade/CEI/statins during follow up, did not influence the importance of CFRdob for prediction of CE (for CFRdob: $exp(b)=0.07$, $p=0.01$ and $exp(b)=0.02$, $p=0.01$ respectively).
Conclusion: Functional evaluation of LIMA/LAD territory by noninvasive CFRdob provides important information for CE in pts post CABG which is independent from the respective Dob-echo or SPECT outcome, as well as from LV function.

P2841 Coronary flow reserve and brachial artery reactivity in patients with chest pain and "false positive" exercise-induced ST segment depression

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Normal coronary arteries may coexist with a physiologically significant impairment in coronary flow reserve (CFR) and with systemic endothelial dysfunction. Aim of this study was to establish the ultrasonically assessed CFR and systemic endothelial function correlates of exercise-induced "false positive" ischemic-like ST segment depression. We studied 13 control subjects and normal coronary arteries (Group 1, controls), and 53 patients with history of chest pain, positive (>1.5 mm) exercise-electrocardiography test and angiographically normal coronary arteries (Group 2, microvascular angina). All patients underwent stress echocardiography prior to angiography. After angiography, CFR and endothelial function were assessed on different days and in random order. Transesophageal (n=16) or transthoracic (n=50) echocardiographic evaluation of left anterior descending coronary artery peak diastolic flow was performed at baseline and following vasodilatory stimulus (dipyridamole up to 0.84 mg/kg in 10 min). Brachial artery flow-mediated vasodilation (FMD) was assessed by measuring the change in brachial artery diameter in response to hyperemic flow by high frequency vascular ultrasound. All patients had normal resting and stress induced left ventricular function by 2D - echocardiography. Controls showed higher values of CFR than patients with microvascular angina did (Group 1=3.2±0.3 vs Group 2=2.3±0.6, $p<0.0001$). FMD was lower in patients with microvascular angina (Group 1= 11.7±1.5% vs Group 2= 4.2±3.4%, $p<0.01$). There was a weak, albeit significant, correlation between CFR and FMD ($r=0.33$, $p<0.01$). Conclusion: ischemic-like stress-induced ST segment changes may be associated to a physiologically significant, but extremely variable reduction in CFR and systemic endothelial dysfunction in patients with normal coronary arteries.

P2842 Combined assessment of contractility and flow reserve in patients with prior coronary bypass surgery by dipyridamole echocardiography

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Recent advance in ultrasound systems enables measurement of coronary flow reserve (CFR) of mammary artery and saphenous vein coronary artery bypass grafts (CABG) using transthoracic Doppler echocardiography (TTDE). However little is known about the relationship between the hyperemic response and regional asynergy induced by stress echo. We evaluated 106 consecutive patients (83M/23F; mean age 67±14 years) scheduled for coronary angiography because of recurrent ischemia after CABG surgery. After evaluating the segmental left ventricular wall motion using tissue harmonic imaging, mammary artery grafts were assessed placing a 5-7 MHz probe in the supraclavicular area sampling the graft flow few cm distal to the takeoff from the subclavian artery. Saphenous vein grafts to left anterior and circumflex coronary artery were detected in the area anterior to the right ventricular outflow; grafts to the right coronary artery were detected anterior to the right ventricular wall with the patient in right lateral decubitus. Dipyridamole (0.84 mg/Kg/8 min) and atropine (1mg) were administered. CFR (ratio of the hyperemic to baseline peak diastolic velocity) <2.0 and <1.6 was considered abnormal for arterial and saphenous grafts, respectively. All patients underwent coronary angiography 2-48 hours after stress echo. CFR feasibility was 94.5%. Wall motion analysis was feasible in 95.9%. Abnormal CFR showed 98% sensitivity, 83% specificity and 89.7% accuracy for the detection of significant (>70%) graft or distal recipient artery stenosis. Stress-induced wall motion abnormalities had 87% sensitivity, 97% specificity and 88.1% accuracy for significant stenosis. False positives of CFR were found in diabetic and hypercholesterolemic patients who had reduced vasodilating capacity and in presence of poor distal runoff of the recipient artery. Inaccauracies of stress echo were observed in presence of baseline wall motion abnormalities, conduction disturbance, blunt pressure and heart rate response to stressors. In 11 patients findings of both techniques integrated to achieve a correct diagnosis. In conclusion the simultaneous assessment of CFR and contractility by TTDE dipyridamole echo is highly feasible and allows to increase significantly the sensitivity and the accuracy of the test.

P2843 Coronary flow reserve by tranthoracic stress echo: adenosine or dipyridamole?

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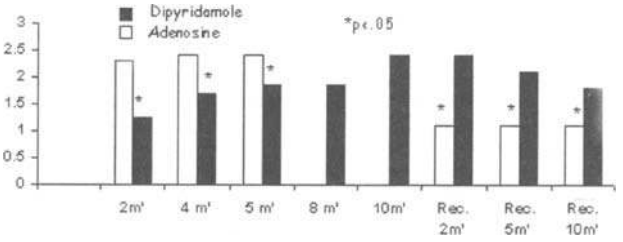
Background: Coronary flow reserve (CFR) is a key physiological parameter which can be evaluated noninvasively with unsurpassed temporal resolution by transthoracic echocardiography (TTE) during vasodilator stress. Aim: To assess the entity, time course and feasibility of TTE assessment of CFR with high dose adenosine (ADO) and dipyridamole (DIP).
Methods: Starting June 2001, 16 patients (9 females; age=58±12 years) with angiographically normal coronary arteries were referred for stress echocardiography. In all, TTE (S8 or S12 probe, HP 5500, Agilent technology) evaluation of distal left anterior descending (LAD) coronary artery was attempted at baseline and following dipyridamole (0.84 mg/kg over 8') and adenosine (140 mcg/kg in 5'), within 24 hours. Wherever color-coded LAD blood flow from the baseline could not be obtained, contrast enhancement with Levovist (Schering AG) was used. Peak diastolic coronary flow velocity of LAD was recorded by pulsed Doppler under the guidance of Color Doppler flow mapping. CFR was calculated as the ratio of dipyridamole/rest peak diastolic flow velocity.
Results: Values of coronary flow reserve over time are reported in figure.



CFR values over time.

Conclusion: High dose ADO and DIP elicit similar and high coronary vasodilatory response, more long- lasting with DIP, which is therefore ideally suited for prolonged acquisition times and integrated imaging modalities requiring sampling on different coronary arteries and/or of different parameters (wall motion and coronary flow).

P2844 Use of transthoracic Doppler assessment of coronary flow reserve for 6 month follow-up post percutaneus coronary intervention

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Background: Advances in ultrasound equipment enable measurement of coronary flow reserve (CFR) of the left anterior descending artery (LAD) with transthoracic second harmonic Doppler echocardiography (TTHDE). CFR at rest and after pharmacologically induced vasodilatation and with contast enhancement could assessed the presence of a significant (>70%) LAD stenosis. Sensitivity and specificity of commonly used noninvasive methods are not satisfying in detecting restenosis after percutaneus coronary intervention (PCI).
Purpose: We have therefore tested the ability of TTHDE technique to be precise noninvasive method to control the angiographic patency of the LAD during 6 month follow-up.
Methods: In 30 consecutive patients (pts) age 56,5±7,2 years, after coronary angiogram confirming severe LAD stenosis, TTHDE was performed. Control measurement was done post PCI and final evaluation 6 months later or during recurrent ischemia. This final evaluation was followed by control CA. Echocardiogarphy was performed with Acuson Sequoia unit by use of broad band transducer with second harmonic capability (3v2c). Each pts underwent a color-guided pulsed-wave Doppler recording of coronary blood velocity in LAD in baseline conditions and after dipyridamole administration. The Doppler signal was enhanced by echo-contrast agent Levovist (Schering). Contrast infusion was performed both before and after dipyridamole. The normal CRF value known from the previous studies is >2,0. All CA results were blinded to TTHDE performing team.
Results: All pts had abnormal CFR values before PCI - both for mean systolic velocity (MSV) and peak systolic velocity (PSV), 1,35±0,6 and 1,49±0,4 respectively. During follow-up 9 pts had recurent ischemia, 7 had patological MSV and PSV values with restenosis confirmed with CA in 6. Those pts were included to group A - with restenosis and 24 others to group B - without. In group A CFR increased after PCI from 1,13±0,22 to 2,66±0,85, p=0,15 and in group B from 1,54±0,37 to 2,82±0,56, p=0,0003. Nonsignificant CFR increase post procedure could be a predictive factor of restenosis.
Conclusions: The sensitivity of TTHDE assessment of LAD patency in 6 month follow-up was 100%, specificity 97%, being most accurate noninvasive method for monitoring LAD patency post PCI. We conclude that statistically nonsignificant CRF increase after PCI could be a predictive factor of restenosis, that could bring useful clinical information for prognosis and clinical decision making e.g. planned rePCI with stent deployment.

P2845 Coronary flow velocity reserve of the left circumflex coronary artery with transthoracic second harmonic Doppler echocardiography

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Background Coronary flow velocity reserve (CFR) assessment is a clinically useful method to assess coronary function. It has been assessed as CFR by noninvasive methods with a transthoracic doppler echocardiographic (TTDE) probe. we can assess CFR in the anterior decending coronary artery by TTDE. The purpose of this study is to evaluate the feasibility in the assessment of CFR in the left circumflex coronary artery (LCX) by TTDE.
Methods We studied 11 patients who underwent coronary angiography. With TTDE, diastolic coronary flow velocity in the proximal LCX were recorded at rest and during hyperemia induced by intravenous infusion of adenosin (0.14 mg/kg/min) under the guidance of color Doppler flow mapping. Intravascular velocity mesurement in the proximal LCX was attained by Doppler guide wire at rest and after hyperemic stimulas by intravenous infusion of adenosin. We compared CFRs for peak and mean diastolic coronary flow velocities (PDV and MDV) determined by TTDE to Doppler flow wire (DFW).
Results There was close agreement between CFRs for peak and mean diastolic velocity by TTDE and DFW (CFR for MDV; r=0.872, p=0.0001. CFR for PDV; r=0.810, p=0.0014.). The peak and mean diastolic coronary flow velocities at baseline determined by TTDE was not correlated to those determined by DFW significantly.
Conclusions Transthoracic echo Doppler with the harmonic mode is a feasible for assessing diastolic CFR.

P2846 Noninvasive assessment of coronary flow reserve by intravenous myocardial contrast echocardiography: comparison with magnetic resonance imaging

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Data from our working group suggest that quantitative myocardial perfusion imaging is feasible by magnetic resonance imaging (MRI). The aim of the present study was to assess feasibility and reliability of measurements of coronary flow reserve (CFR) performed with intravenous echocardiographic myocardial perfusion imaging (EMPI) by comparison to MRI measurements of CFR in the same individuals.
Methods: 10 healthy volunteers (24±4 years, 7 male) underwent adenosine stress testing at two occasions: MR perfusion imaging using saturation recovery T1 based spin-labeling technique (SRTFL) and EMPI. During EMPI, before and during infusion of 140µg/kg/min adenosine up to 15 loops of the 3 apical standard views were stored digitally (HDI 5000, ATL Philips) during infusion (90ml/h) of the transpulmonary contrast agent SonoVue (Bracco Byk-Gulden). To avoid contrast destruction during real time imaging, low emission power (MI 0.12-0.18) and a contrast specific imaging modality, power pulse inversion, was used. Non linear curve fitting (y=A*(1-e(-beta*t)) of the replenishment in a representative septal segment provided the value beta, which describes the deflection of the curve. ECHO-CFR was calculated as the quotient of the value beta during adenosine infusion and at rest, respectively. MRI-CFR was evaluated from absolute quantitative perfusion using two-compartment model analysis.
Results: Adenosine infusion was well tolerated by all participants. The EMPI data of one volunteer was not evaluable due to insufficient image quality. Mean beta at rest was 0.3±0.4 s-1 and 0.85±0.6 s-1 during adenosine stress. Mean ECHO-CFR was 3,23±1.1 and showed a close correlation with MRI-CFR. The value A (plateau) showed a higher diversity (0.7-4.0 at rest, 1.8-9 during adenosine stress) compared to beta and a worse correlation with MRI results.
Conclusion: Assessment of CFR by contrast perfusion echocardiography is feasible and results correlate well with MRI-CFR given by quantitative spin-labeling perfusion measurement.

P2847 Transthoracic echocardiographic assessment of coronary artery flow and reserve in the 3 major coronary arteries: feasibility and results

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Background: Coronary flow reserve (CFR) can be measured by transthoracic echocardiography (TTE) during vasodilator stress on mid- distal left anterior descending (LAD). Left circumflex (LCx) and Posterior Descending (PD) have remained off- limits for this technique so far. **Aim:** To assess the feasibility and results of TTE assessment of CFR in the 3 coronary arteries. **Methods:** Starting June 1 2001, 66 consecutive patients (42 males; age=64 ±12 years) were referred for stress echocardiography. In all, TTE (S8 probe, second harmonic 7 MHz, HP 5500, Agilent technology) imaging of 3 coronary arteries was attempted. Mid - distal LAD coronary artery was imaged from a modified apical two-chamber view; PD artery from apical 2- chamber with counterclockwise rotation and anterior angulation of the transducer; LCx from apical 4- chamber with a clockwise 50 - 80 degrees rotation from LAD imaging and posterior angulation of the transducer. Wherever color-coded blood flow from the baseline could not be obtained, contrast enhancement with Levovist (Schering AG,300 mg/ml/min) was used. Peak diastolic coronary flow velocity of each coronary artery was recorded by pulsed Doppler under the guidance of Color Doppler flow mapping. CFR was calculated as the ratio of dipyridamole/rest peak diastolic flow velocity. **Results:** Interpretable signals (at baseline and during stress) were observed in 65 patients for LAD, 35 for LCx and 44 for DP, yielding a feasibility of 98, 53 and 66% respectively. The time needed for successful coronary artery imaging was 92±18 s for LAD, 350±30 for LCx and 260 ±33 s for PD. In the 27 patients with angiographically confirmed normal coronary arteries and interpretable signals from all 3 arteries, CFR values were not different on LAD (2.5±0.4), LCx 2.5±0.5(p=ns) and PD (2.5±0.5; p=ns). **Conclusion:** With last generation, high frequency,second-harmonic, contrast-enhanced transthoracic echocardiography, imaging of coronary artery flow and assessment of flow reserve can be feasible in all major coronary arteries.- albeit with different success rates, highest for LAD and lowest with LCx. In the absence of epicardial coronary artery disease, coronary flow reserve values are comparable in the 3 coronary arteries.

P2848 Long-term prognostic value of pharmacological stress echocardiography in diabetics patients: a single center experience

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Patients (pts) with diabetes mellitus have an increased risk of cardiovascular morbidity and mortality. Data on the prognostic value of pharmacological stress echocardiography (PSE) in diabetic pts are still lacking. The purpose of this study was therefore to assess the prognostic significance of PSE and its incremental role in diabetics pts with known or suspected coronary artery disease. **Methods:** We studied 325 diabetics pts who underwent PSE with either Dobutamine (185 pts) or Dypiridamole (140 pts) in our institution from July 1995 to December 2000. 12 pts who underwent coronary artery revascularization within 3 months from the PSE, and 10 lost to follow-up were censored. Pts outcome and clinical evaluation for the presence of cardiac risk factors were finally assessed in 303 pts through review of patient's hospital record or by phone interview, for a mean period of 32.9 (range 4-60) months. Spontaneous hard events (death; combined endpoint: death + myocardial infarction) were considered as endpoints. **Results:** no major complication occurred during the tests. The PSE was positive in 122 pts (40.3%). During the follow-up 75 hard events occurred, including 40 death (13.2%) and 35 non-fatal acute myocardial infarction (11.5%). At univariate analysis, the following variables resulted significantly predictive for hard events (in descending order): peak stress left ventricular ejection fraction (peak EF) < 40%, wall motion score index (WMSI) at rest, PSE time duration, previous myocardial infarction, age and positive PSE for ischemia. By multivariate analysis, the combination of clinical and stress test variables identified age, peak EF < 40% ($p<0.001$) and PSE duration ($p<0.01$) as strongest independent predictors of cardiac death (global chi-square: 68.3; $p<0.0001$). On the other hand, peak EF ($p<0.001$), WMSI at rest and previous myocardial infarction appeared to be the only independent determinants of the combined endpoint (global chi-square: 58.2; $p<0.0001$). The mean survival time free of hard cardiac events was 43.9 months in pts with peak EF < 40%, and 55.4 months in pts with peak EF > 40% (Log Rank:12.4; $p < 0.0005$). **Conclusions:** our findings suggest that different DSE variables should be considered when assessing the likelihood of future events in diabetic pts. A PSE response positive for ischemia does not predict a worse outcome in diabetic pts. Conversely, global left ventricular function at peak stress is the strongest independent predictor of hard cardiac events, combined with other clinical and echo variables.

P2849 Prognostic information of left ventricular dilation in those patients with a positive stress echo

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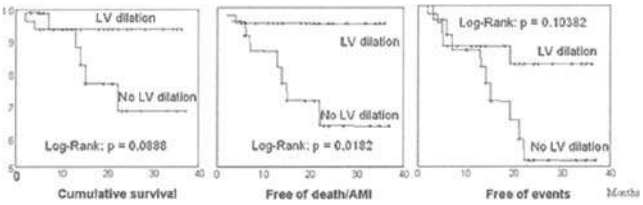
It is well known that left ventricular dilation in those patients during stress echo is a sign of ischemia. Our aim was to analyze if among those patients with a positive stress echo result, left ventricular dilation is associated with a worse long-term prognosis.

Patients and methods: 63 patients undergoing stress echo (29 dypiridamole, 22 dobutamine, and 2 adenosine) in which test showed positivity at echocardiography were studied. Patients were followed-up during a mean of 18±10 months. Left ventricular dilation during stress echo was defined as the presence of increasing in left ventricular end-diastolic volume measured at apical 4-chamber view. The outcome of patients with and without left ventricular dilation was compared (Kaplan-Meier survival curves, that were compared with the Log-Rank test).

Results: Mean age was 68±9 years, and 76% were male gender. During stress echo, end-diastolic left ventricular volume decreased from 96±37 to 87±40 ml (paired t-test: $p = 0.003$), and end-systolic volume from 44±28 to 39±27 ml ($p = 0.004$). Left ventricular dilation occurred in 23 patients (36.5%). Prognosis at 3-years was worse in patients with left ventricular dilation: Cumulative survival 69±12% vs. 95±3.5% (Log-Rank: p=0.0888), probability of being free of death and myocardial infarction 62.9±11.7% vs. 95±3.5% (Log-Rank: p=0.0182), and free of any event (death, infarction, revascularization or admissions due to angina or cardiac failure) 52.4±11.9% vs 87.5±5.2% (Long-Rank: $p = 0.1038$) (see figure).



Prognosis after stress echo.

Conclusion: Left ventricular dilation is not only an indirect sign of ischemia during stress echo. Left ventricular dilation implies by itself a worse long-term prognosis among those patients with a positive stress echo.

P2850 Validation of a model for prediction of all causes of mortality by exercise echocardiography

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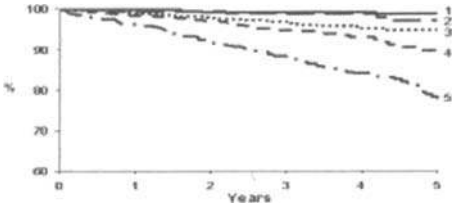
Rationale. The aim of this study was to validate a model for prediction of mortality by combined clinical, exercise stress and echocardiographic data.

Methods: We studied 5679 patients (age 62 ± 12 years, 3231 men) who were followed up for a mean of 3 years after treadmill exercise echocardiography. Patients were randomly divided into 2 groups of equal size: 1) The modeling group; In these patients multivariate analysis was performed using clinical, exercise stress ECG and echocardiographic data to define independent predictors of mortality. To determine parameter coefficients, 300 bootstrap resamplings were performed. Patients were divided into 5 risk categories according to their composite score. Survival rate in each of these risk categories was estimated by kaplan-Meyer method. 2) The validation group. In this group, the risk model was applied. Patients were divided into 5 risk categories based on data obtained from the modeling group.

Results: During follow-up, there were 315 deaths (151 in the modeling group). Independent predictors of mortality in the modeling group were exercise wall motion score index ($\chi^2 = 22.4$, $p < 0.0001$), workload ($\chi^2 = 17.1$, $p < 0.0001$), male gender ($\chi^2 = 15.4$, $p<0.0001$) and age ($\chi^2 = 5.5$, $p=0.02$). Survival curves in each of the predefined risk categories in the validation group are shown in the figure.



Mortality in the validation group according to risk factor.

Conclusion: This study provides a model for categorical risk assessment by combining clinical, exercise stress and echocardiographic data.

P2851 Prognostic value of noninvasive pacemaker stress echocardiography in patients with permanent pacemakers: a multicenter study

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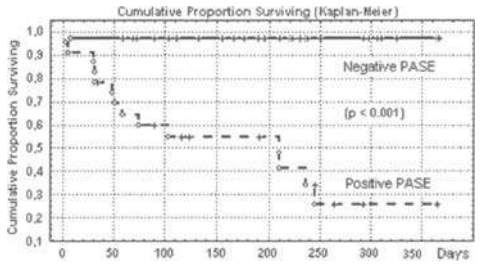
Background: Noninvasive pacemaker stress echocardiography is an effective option for noninvasive diagnosis of coronary artery disease (CAD) in the expanding population of patients with permanent pacemakers.
Aim: To investigate the value of pacemaker stress echocardiography in risk stratification of patients with permanent pacemakers and suspected CAD.
Methods: Fifty seven patients (41 men, age 66 ± 11 years) with permanent pacemakers underwent noninvasive pacemaker stress echocardiography by external programming (10 bpm increment up to ischemia or target heart rate) to evaluate suspected or known coronary artery disease. All 8 contributing laboratories passed the quality control for stress echo reading before entering the trial. All patients have follow-up for 6 ± 3 months. Both soft (coronary revascularization, unstable angina) and hard (myocardial infarction, cardiac death) end points were recorded and analyzed.
Results: Pacing stress was well tolerated and echo images were interpretable in all patients. A positive echocardiographic result (evidence of ischemia) was detected in 23 (40%) patients. During follow-up, there were 3 cardiac deaths, 2 myocardial infarctions, 4 unstable angina and 8 coronary revascularizations. The overall event-free survival was 39% in the ischemic group and 97% in the nonischemic group ($p<0.001$)(Picture). In a multivariate analysis positive result of stress echocardiography was independently associated with increased risk of end points (hazard ratio = 11.9; 95% confidence interval: 5.5 to 18.3; p = 0.01).



Pacing stress echo and prognosis.

Conclusions: In patients with permanent pacemakers and suspected or known CAD a positive noninvasive pacemaker stress echocardiography is a strong prognostic predictor.

P2852 Early low-dose dobutamine echocardiography in patients with acute myocardial infarction treated with facilitated percutaneous coronary intervention-preliminary results

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Facilitated percutaneous coronary intervention intervention (PCI) combines pharmacotherapy (reduced dose thrombolysis and full dose platelet GP IIb/IIIa inhibitor) and immediate PCI in acute myocardial infarction (AMI).
The aim of this study was to evaluate global and regional contractile function at rest and contractile reserve during dobutamine echocardiography (DE) in patients with AMI treated with facilitated PCI.
Data of 90 pts (70% males, 30% females, mean age 56,84 ± 9,9 years) were analyzed, 11(12,2%) had prior MI, 7(7,8%) in a different region, 4(4,5%) in the same region. All pts received in local hospitals intravenous thrombolytic therapy (rt-PA 15mg bolus + 60-min infusion of 35 mg) and intravenous GP IIb/IIIa inhibitor (abciximab 0,25mg/kg bolus + 12-h infusion 0,125μg/kg/min). PCI was performed after immediate transfer of pts to a regional cardiology center with a Cathlab. Mean transfer time was 76 ± 25 min.
Echocardiography was performed 3,6 ± 1,7 days after AMI. Contractility was assessed using a 16-segment model and wall motion score index (WMSI) was calculated. A contractile reserve was defined as an improvement of wall motion by at least 1 grade in 2 or more contiguous segments during dobutamine infusion (5-15μg/kg/min).
At baseline regional contractility was normal in 10 (11,1%) pts. From the visible 1420 segments 68,7% were normokinetic, 16% hypokinetic, 14,7% akinetic, 0,5% dyskinetic. Preserved left ventricular (LV) function defined as ejection fraction (EF)>50% was observed in 74 (82,2%) pts. Mean EF was 57,8±9,2%. DE was performed in 69 (76,6%)pts. During DE significant improvement of regional contractility and WMSI was observed (1,509±0,28 at baseline to 1,316±0,28 at maximal dose of dobutamine; p<0,0001) (table). A contractile reserve was observed in 49 pts(71,01%). No major adverse events during DE occurred.

	WMSI p<0,0001	Seg. analyzed	Normokinetic	Hypokinetic	Akinetic	Dyskinetic
Baseline	1,509	1093	712 (64,1%)	197 (18%)	183 (16,7%)	1(0,1%)
Dobutamine Echocardiography	1,316	1091	853 (78,2%)	132 (12,1%)	105 (9,6%)	1(0,1%)

Conclusions: Early low-dose dobutamine echocardiography is a safe way to assess contractile reserve in patients with AMI and patent infarct-related artery. A high percentage of patients with AMI treated with facilitated PCI have well preserved LV function and contractile reserve.

P2853 Real time myocardial contrast echocardiography predicts left ventricular wall motion recovery after reperfused acute myocardial infarction

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Real time myocardial contrast echocardiography (RT-MCE) is a recently developed method that avoid some of the limitations of intermittent triggered imaging. We sought to determine whether: 1) perfusion by RT-MCE would predict recovery of LV function after acute myocardial infarction (AMI), and 2) data are comparable to perfusion by Technetium-99m-sestamibi single photon emission computed tomography (SPECT) and contrast-enhanced magnetic resonance (CMR).
Methods: We studied 34 consecutive patients (pts) with AMI submitted to percutaneous transluminal coronary angioplasty. MCE was performed (up to 3 intravenous slow injections containing 1 cc of Optison and 9 cc of saline each) 6±3 days after AMI. 2-dimensional echocardiography (2-DE) was performed at the time of the MCE study and at follow-up (9±2 weeks) to measure wall motion score index (WMSI). SPECT and CMR were performed before discharge in 16 and 5 pts respectively. A 10-segment LV model was used for perfusion analysis, scoring 0=absence of perfusion; 0.5=partial perfusion; and 1=complete perfusion. Regional (AMI-related territory) and global WMSI were calculated using a 16-segment model.
Results: Follow-up 2-DE was available for 32 pts that were subdivided in 2 groups: Recovery (RG) (n=22) and no recovery group (NRG) (n=10). No significant differences in clinical, angiographic and 2-DE variables were found between groups at baseline. Global and regional WMSI improved from 1.5±0.3 to 1.2±0.2 ($p<0.001$) and from 1.9±0.5 to 1.5± 0.4 ($p<0.001$) in the RG, and impaired from 1.5±0.3 to 1.6±0.2 ($p<0.05$)) and from 1.9±0.5 to 2.0±0.4 ($p=0.06$) in the NRG. Regional and global MCE perfusion score were 0.8±0.3 and 0.9±0.1 in the RG; and 0.5±0.4 and 0.7±0.3 in the NRG ($p=0.06$ and $p=0.11$, respectively). Intersegment concordance for perfusion defects between RT-MCE and SPECT was 81% ($p<0.001$, k= 0.38) and between RT-MCE and CMR was 77% ($p=0.29$, k=0.17). A regional perfusion score >0.65 was the more accurate RT-MCE value to predict LV recovery with positive predictive value of 81% and negative predictive value of 60% ($p<0.05$).
Therefore, RT-MCE has high positive predictive value for recovery of LV function after reperfused AMI.

P2854 Microvascular status after acute myocardial infarction: the effect of no-reflow in patients treated with primary PTCA or intravenous thrombolysis

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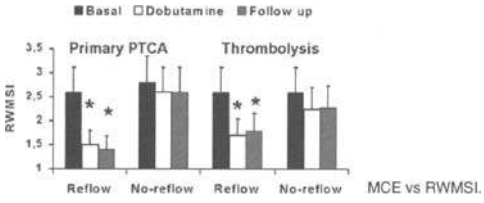
Background: In patients with acute myocardial infarction (AMI), early recanalization obtained with thrombolysis or primary PTCA, results in smaller infarcts and better clinical outcome. However, despite early recanalization, some patients suffer from microvasculature damage (no-reflow phenomenon). This study aimed to verify the effect of no-reflow on clinical outcome in patients treated with primary PTCA or intravenous thrombolysis.
Methods: We studied 55 patients with a first AMI (21 treated with primary PTCA and 33 with intravenous thrombolysis, all with no residual stenosis in the infarct artery) with: basal echocardiogram on the first day and at 90-days follow-up, intravenous myocardial contrast echocardiography to assess microvascular perfusion 2.1±1.3 days after AMI and low dose dobutamine echocardiography 3.8±1.6 days after AMI. Regional wall motion score index (RWMSI) analysis was performed in all echocardiographic studies.
Results: Patients with microvascular reflow at contrast echocardiography showed RWMSI recovery from basal to dobutamine and follow up both when treated with primary PTCA (2.6±0.4 vs 1.5±0.4 vs 1.5±0.5, *p<0.001) or with thrombolysis (2.6±0.2 vs 1.7±0.5 vs 1.8±0.5, *p<0.001). In all patients with No-reflow phenomenon the RWMSI did not change significantly.



Conclusion: The presence of microvascular reflow at contrast echocardiography predicts RWMSI recovery at dobutamine and follow up echocardiography, independently from thrombolytic or PTCA therapy.

P2855 A comparison between intracoronary and intravenous myocardial contrast echocardiography in the study of myocardial viability after acute myocardial infarction

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Aim: This study sought to determine serial changes in microvascular integrity using myocardial contrast echocardiography (MCE) in patients with acute myocardial infarction (AMI). In addition, the aim of study was to define the optimal time for assessing microvascular integrity to predict late recovery of LV regional function.
Patients and methods: We studied 43 pts (40 male, mean age 52 years) with first AMI who underwent successful primary coronary angioplasty. The study protocol included the acquisition of intracoronary MCE shortly after reflow (15 minutes), intravenous MCE two days and 15 days later. Regional wall motion (RWM) was assessed by 2D-echo 6 months later. Intravenous MCE was performed with venous Levovist administration and intermittent Harmonic Power Doppler (HPD). In each pt the contrast score index (CSI) for the infarct related area was calculated according to the standard protocol.
Results: A total of 220 segments of the infarct related area were analysed. In the table is shown myocardial perfusion on a segment by segment basis as detected by MCE at different time. A change in microvascular perfusion at 15 days MCE was detected in 76 segments (34%): an improvement in myocardial perfusion was detected in 46 segments (suggesting recover of microvascular dysfunction), while a contrast defect newly appeared in 30 segments (suggesting a progressive miscrovascular damage). Mean CSI was 0,69±0,26 (intracoronary MCE); 0,74±0,22 (2 days MCE) and 0,69±0,30 (15 days MCE). At 6 months follow-up a statistically significant correlation was found between intracoronary CSI and RWM variation (r 0,35; p< 0.05); between 2 days CSI and RWM variation (r 0,44; p< 0.01) and between 15 days CSI and RWM variation (r 0,75; p< 0.0001).

	intracoronary MCE	2 days MCE	15 days MCE
normal perfusion	131	113	128
moderate perfusion defect	39	78	69
severe perfusion defect	50	29	23

MCE: myocardial contrast echocardiography

Conclusions: microvascular damage after reperfusion may be either reversible or progressive and may occur even after 2 days. Late assessment of myocardial perfusion (15 days MCE), when microvascular damage has reached his final and full extent, best predicts recover of function.

P2856 Use of myocardial contrast echocardiography in identifying patients with failed reperfusion after thrombolysis in acute myocardial infarction

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Background: The diagnosis of failed reperfusion after thrombolysis still remains a daily unsolved issue. At present, the decision of different level of aggressiveness in treating acute myocardial infarction (AMI) is only based on clinical, enzymatic and ECG data. The role of intravenous myocardial contrast echocardiography (MCE) in the assessment of the efficacy of reperfusion therapy is still being evaluated.
Method: At this aim, 22 consecutive patients with AMI, treated with iv t-PA within 6 hours from symptom onset, underwent, on day one after reperfusion therapy, coronary angiography and MCE using real-time Power Modulation Imaging (Philips, Sonos 5500) during continuous infusion of SonoVue® (Bracco). A prototype (Bracco Imaging) rotating infusion pump at 120-180 ml/h infusion rate was used. According to TIMI myocardial perfusion grade, patients were divided into two groups: Group A (n = 16) TIMI grade 0-1 and Group B (n= 6) TIMI grade 2-3. The endocardial length of residual contrast defect (apical 4- 5- and 2- chamber views) after thrombolysis, contrast score index (3 grade scale) and clinical markers of reperfusion were calculated. Successful reperfusion after iv t-PA was defined as an early (<12h) peaking of creatine kinase and a rapid decrease of at least 50% of ST-segment elevation (within 2 h after thrombolysis), and as a residual MCE perfusion defect < 10%. Left ventricular ejection fraction and wall motion score index on day 1 were also calculated.
Results: Patients in group A and B had similar ejection fraction and wall motion score on day 1 (46±6% vs 45±8%, and 1.8±0.4 vs 1.5±0.3, respectively, ns). On the contrary, the contrast score index and the extent of contrast defect were significantly higher in group A as compared to group B (3.6±0.3 vs 3.2±0.2, p<0.03, and 30±8% vs. 4±6%, p<0.001, respectively). Failed reperfusion (TIMI grade 0-1) was correctly identified by clinical criteria (ECG+enzyme) in 12/16 patients, and by MCE criteria in 16/16 patients. Thus, MCE showed higher predictive values of failed reperfusion as compared to clinical markers (PPV 100%, NPV 67%, vs 85% and 50%, respectively)
Conclusions: Real-time perfusion imaging with SonoVue® can accurately determine reperfusion success at tissue level and may be an important adjunctive tool for a better indication to a more aggressive treatment in AMI

P2857 Effects of rescue PTCA after acute myocardial infarction on tissue level perfusion: a myocardial contrast echocardiography study

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Background: The clinical usefulness of rescue PTCA in patients with acute myocardial infarction (AMI) is still under discussion. In particular, no data are available on the effects of late infarct-related artery (IRA) reopening on microvascular perfusion. Echocardiographic assessment of microvascular integrity is now feasible by intravenously injected contrast agents and real time myocardial contrast echocardiography (rt-MCE). Previous MCE studies showed the efficacy of primary PTCA in reducing microvascular damage. We sought to determine if even rescue PTCA may improve tissue level perfusion

Method: We studied 14 patients with first anteroseptal AMI, treated with iv t-PA within 6 hours from symptom onset, undergoing on the basis of clinical symptoms left anterior descending (LAD) angioplasty, within 12 and 24 h after thrombolysis. MCE was performed using real-time Power Modulation Imaging (Philips Sonos 5500) during continuous infusion of SonoVue® (Bracco). A prototype (Bracco Imaging) rotating infusion pump at 120-180 ml/h infusion rate was used. The endocardial length of contrast defect (apical 4- 5- and 2- chamber views), the contrast score index (3 grade scale) after thrombolysis and soon after rescue PTCA, were calculated. Left ventricular ejection fraction and wall motion score index were also calculated before LAD reopening.

Results: In all selected patients coronary angiography showed a TIMI myocardial perfusion grade 0-1 after thrombolysis and a successful LAD reopening (TIMI grade 3) after rescue PTCA. In 71% (10/14) of patients a significant reduction in contrast score index and in the length of contrast defect was observed after rescue PTCA (3.6±0.2 vs 3.1±0.3 and 35±11% vs 14±10%, $p<0.005$, respectively), whereas in the remaining 29% (4/14) a slight increase in microvascular damage was found (3.6±0.1 vs 3.8±0.3 and 30±11% vs 32±10%, ns, respectively). The two groups of patients had similar contrast score, length of contrast defect, ejection fraction, wall motion score and coronary artery disease severity before coronary revascularization.

Conclusions: This study shows that MCE may play a crucial role in acute coronary syndrome. Our preliminary data suggest that in the majority of patients, even rescue PTCA in still unstable patients after thrombolysis may be effective in reducing microvascular damage. Larger studies are needed to better understand the main determinants of the successfully myocardial flow restoration after late IRA reopening

P2858 Real time myocardial contrast echocardiography early after acute myocardial infarction accurately predicts late functional recovery

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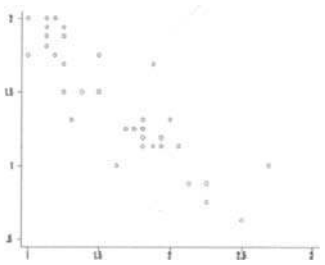
Background: Microvascular integrity is a pre-requisite for ensuring viability early after acute myocardial infarction (AMI). Myocardial contrast echocardiography (MCE) can be used to detect presence of intact microvasculature and hence viable myocardium. Real-time MCE is a relatively simple and new bedside technique that may be utilised to identify viable myocardium.

Methods: 50 patients underwent Real-time MCE using Optison® one week after AMI. Myocardial perfusion (2= homogeneous, 1=reduced, 0=absent) and wall motion (1=Normal, 2=hypokinetic, 3=akinetic) were assessed at baseline using a 16- segment LV model. Contrast score index (CSI) representing global perfusion was also calculated at baseline. Both regional and global wall motion were re-assessed after 3 months.

Results: Of the 93 dysfunctional segments that showed functional recovery, MCE had demonstrated homogeneous perfusion in 65 segments (70%)at baseline. Of the 204 segments that failed to recover, MCE showed reduced perfusion in 192 segments (94%). Thus the positive and negative predictive values of MCE for predicting late functional recovery were 84% and 87% respectively. There was an excellent correlation ($r= 0.91$, $p<0.001$) between global perfusion (CSI) at baseline and recovery of global LV function assessed by wall motion score index (WMSI) [see fig.1]



Conclusion: Real time MCE is an accurate bedside technique to identify viable myocardium post AMI. This technique may be utilised to reliably predict late recovery of function in dysfunctional myocardium after AMI.

P2859 Prediction of mortality in patients with complete right bundle branch block. A multicenter stress echocardiography study

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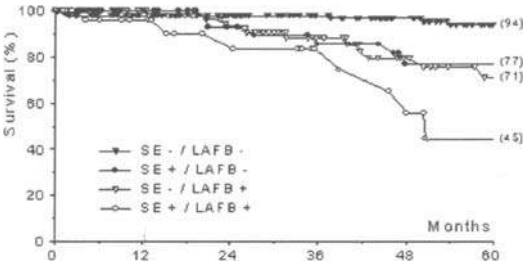
Complete right bundle branch block (RBBB) is an independent predictor of mortality in unselected patients referred to noninvasive evaluation of coronary artery disease (Hesse, Am J Med 2001). Aim of this study was to investigate whether different levels of risk could be assessed in RBBB patients. The study group consisted of 343 RBBB patients (age 66±9 yy; 267 men) who underwent stress echo (SE) with either dipyridamole (n=231) (up to 0.84 mg over 10'+atropine up to 1 mg) or dobutamine (n=112) (up to 40 mgr/kg/min+atropine up to 1 mg) at 8 different italian cardiology centers; 102 (30%) patients also had left anterior fascicular block (LAFB). SE was positive for ischemia (new or worsening of preexisting wall motion abnormality) in 109 (32%) patients. During follow-up (38±32 months), 35 deaths occurred. In addition, 73 patients (48 with ischemia at SE) underwent revascularization and were censored at the time of the procedure. Of 14 clinical, electrocardiographic and echo variables analyzed, ischemia at SE (HR=2.9; 95% CI=1.5-5.7; p=0.002), LAFB (HR=2.8; 95% CI=1.4-5.6; p=0.002), age > 65 years (HR=2.1; 95% CI=1.0-4.3; p=0.047), and resting wall motion score index (HR=2.5; 95% CI=1.0-6.5; p=0.057) were multivariate predictors of mortality. From the interaction of SE result and presence/absence of LAFB, a low-risk group (with neither ischemia nor LAFB), two intermediate-risk groups (with ischemia only, and with LAFB only, respectively), and a high-risk group (with both ischemia and LAFB) were identified (Figure).



Kaplan-Meier survival curves.

In conclusion, an effective stratification of risk can be obtained in RBBB patients by means of SE and LAFB information.

P2860 Exercise stress echocardiography differentiates ischaemic from non-ischaemic dilated cardiomyopathy

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Previous work has shown the usefulness of dobutamine echocardiography to differentiate ischemic dilated cardiomyopathy (IDC) from nonischemic dilated cardiomyopathy (NIDC), but no studies have been made using exercise echocardiography (EE). We hypothesized that most of the patients (pts) with NIDC may have some contractile reserve and therefore increase LV ejection fraction (LVEF) during exercise, as opposed to IDM pts. Between March 1, 1995 and March 1, 2001 we performed 4133 EE studies to 3830 pts. Among 289 (8%) having moderate or severe LV dysfunction (biplane LVEF <41% and left ventricular end-diastolic diameter >5.2 cm), 207 were excluded due to: history of myocardial infarction, 111; scarring on echocardiography (regional akinesia/dyskinesia with thinning and/or increased brightness), 28; previous revascularization procedures, 13; aortic valve disease, 9; known cause of cardiomyopathy, 11; no submission to angiography, 35. The study group was therefore composed of 82 pts encouraged to perform maximal treadmill EE. EE criteria for IDC were either regional wall motion (RWM) impairment or LVEF decrease/no change from baseline to peak exercise, while criteria for NIDC were RWM improvement/no change and LVEF increase. The IDC group was formed by 39 pts having >69% diameter stenosis in a major epicardial coronary artery or major branch vessel. The remaining 43 pts constituted the NIDC group.

Results: The number of coronary risk factors (IDC 2.0±1.1; NIDC 1.9±1.1), baseline LVEF (IDC 30±7; NIDC 30±8) and exercise-induced angina (IDC 23%; NIDC 14%) were not different between groups (p=NS); whereas IDC pts achieved less Mets (6.6±3.1 vs 8.3±2.8, $p<0.05$) and product heart rate x systolic blood pressure x 10^3 (22±5 vs 27±7, $p<0.001$), and developed regional and/or global LV dysfunction more frequently (79% vs 28%, $p<0.001$). Sensitivity, specificity, positive and negative predictive values and global accuracy for IDC detection were 79% (CI: 70-88), 72% (CI: 63-81), 72% (CI: 63-81), 79% (CI: 67-85), and 76% (CI: 69-83), respectively.

In conclusion,a global and/or regional LV function impairment with exercise is accurate to identify patients with IDC. This method may, therefore, reduce the need for invasive procedures

P2861 Dobutamine-stress echocardiography in children: diagnostic value of myocardial ischaemia

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Detection of myocardial ischemia is required in children with congenital, acquired or postoperative coronary artery diseases.The aims of this prospective study were to determine the safety and feasability of DSE in children, and to assess its reliability for detection of myocardial ischemia and coronary disease.

Methods: DSE was performed according to the standard protocol used in adults. Selective coronary angiography and/ or Thallium scintigraphy were performed for comparison. Seventy-five DSEs were performed in 71 patients (31 females, 30 males, median age= 11 years). Cardiac pathologies were: posttransplant monitoring (40 cases), postSwitch operation monitoring (13), abnormal origin of the left coronary artery from the pulmonary trunk (6), Kawasaki aneurisms (6), coronary fistulae (5), left ventricle aneurism (1) and miscellaneous (4). Sixty-two were performed routinely and 13 were motivated by: chest pain (8), dyspnea (2), LV dysfunction (1) or syncope (1). Fourteen were receiving antihypertensive medication but none with beta adrenergic antagonistic therapy.

Results: The maximum dose stage of 40 mcg/kg/mn was reached in 72/75 cases (96%) and 30 mcg/kg/mn in 3 (chest pain). The most frequent clinical side effect was palpitations (15%). Maximum heart rate was 90 to 183/mn (30 to 351% of basal and 43 to 90% of theoretical maximum), with no difference between transplanted and non-transplanted patients. Maximum blood pressure was 100 to 194mmHg (7 to 109% of basal); increase was lower in transplanted versus non-transplanted patients with antihypertensive medication (p= 0.005). No sustained supraventicular or ventricular arythmia, nor significant ST segment change, occurred. Twenty (27%) DSEs were abnormal: 8 posttransplant, 2 Kawasaki, 4 postSwitch, 4 non-operated coronary origin from pulmonary trunk, 1 non-operated coronary fistulae and 1 left ventricle aneurism (15 of them were clinically asymptomatic). DSE sensitivity and specificity were respectively 100% and 76% when compared to Thallium scintigraphy (31 cases) and 70% and 90% when compared to coronary angiography (40 cases).

Conclusion: DSE is safe and well tolerated in children. DSE is probably the best method of monitoring coronary artery disease in children, combining both reasonable sensitivity and specificity without being invasive, requiring hospitalization or engendering significant morbidity.

P2862 Influence of left ventricular geometry, myocardial abnormalities and wall stress on the accuracy of dobutamine stress echocardiography

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Background: Recent work has suggested that the sensitivity of dobutamine stress echocardiography (DSE) is reduced in patients with concentric remodeling, but the cause of this finding is unclear. We sought whether wall stress or myocardial abnormalities could explain the influence of left ventricular (LV) morphology on the accuracy of DSE.

Methods: We studied 161 patients with no wall motion abnormalities at rest (age 60±11 years, 105 men) who underwent DSE and coronary angiography within 6 months, without an intervening event. Echocardiograms were measured for relative wall thickness (RWT), LV chamber size and LV mass. All patients underwent gray scale and color tissue Doppler imaging from three apical views, which were stored and analyzed off line. Increased RWT and increased LV mass were defined as >=0.45 and as >131 g/m^2 in men and >100 g/m^2 in women, respectively. Patients were classified into four groups according to RWT and LV mass; normal geometry, concentric remodeling, concentric hypertrophy and eccentric hypertrophy. Significant coronary artery disease was defined as >=50% stenosis. Circumferential (cESS) and meridional end-systolic wall stress (mESS) at rest and peak DSE were calculated according to previously published methods. Integrated backscatter and strain rate (SR) imaging were used to detect changes in structure and function; average cyclic variation (CV) of integrated backscatter, SR and peak systolic strain were calculated by averaging each segment.

Results: Both false negative and false positive results for DSE were present in 35 patients (22%). The accuracy of DSE in patients with concentric remodeling (61%) was lower than that in patients with normal geometry (85%, $p<0.05$) or concentric hypertrophy (86%, $p<0.05$), and the accuracy with eccentric hypertrophy (64%, $p<0.05$) was lower than with concentric hypertrophy. Although, sensitivity, specificity and accuracy were comparable among each quartile in CV, SR and peak systolic strain, patients with lowest quartile of cESS and mESS at peak DSE had significantly lower sensitivity and accuracy than those in the highest quartile, respectively. Multivariate logistic regression analysis demonstrated that a reduced cESS at peak DSE (p=0.012), presence of concentric remodeling (p=0.044) and eccentric hypertrophy (p=0.012) were significant predictors of both false-negative and false-positive results for DSE.

Conclusions: The accuracy of DSE is influenced by wall stress at peak and the geometric pattern of the LV, but not myocardial abnormalities.

P2863 Factors that have an impact on the interobserver agreement differences for the interpretation of dobutamine stress echocardiograms

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Background: Dobutamine Stress Echocardiography (DSE) is widely used for detection of Coronary Artery Disease. However, there are still some agreement differences between the observers over the interpretation. Identifying factors which impact the interobserver variability will be beneficial for lowering the interobserver differences.
Methods: We therefore evaluated total of 366 randomly selected DSE's from our institution for interpretation by 3 cardiologists who were blinded to each other. Reading agreement was determined as ranging from equal assessment on test positivity and negativity for ischemia by 2 or 3 readers to 3 of 3 readers for each study. Agreement levels were compared to each other with respect to heart rate (HR), blood pressure response, extent and severity of the wall motion abnormality, beta blockers usage, and wall motion score indices (WMSI). Extent was determined by the number of segments with new onset of wall motion abnormalities. Severity was defined by the presence of new wall motion abnormality during peak stress. Heart rate response was accepted as blunted when peak heart rate is less than 85% of age related predicted heart rate. All parameters were compared between agreement groups.
Results: Mean agreement between the 3 readers on normality and abnormality of DSE resulted with a kappa level of 0.55. More extensive and more severe wall motion abnormality during DSE led to better agreement level achievement. Agreement level increased with appropriate heart rate response. See Table.

Factors that have an impact on the interobserver agreement difference for the interpretation of dobutamine stress echocardiograms

	3 out of 3 readers	2 out of 3 readers	P
Rate pressure product(10 3 mmHg min-1)	25.5 ± 5.8	19.7 ± 8.1	0.01
Extent (Segments)	3.2 ± 2.8	2.2 ± 1.8	0.05
Severity	26%	8%	<0.001
Beta-blocker	9%	34%	<0.001
WMSI	1.5 ± 0.4	1.2 ± 0.2	0.06

Conclusion: Major determinant of disagreement between observers during DSE is inadequate heart response. Cessation of beta-blocker prior to DSE and perhaps more liberal use of atropine will lead to better interobserver agreement.

P2864 Myocardial contrast echo and radionuclide scintigraphy in patients with left bundle branch block with or without coronary arteries disease

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Background: The association between left bundle branch block (LBBB) and coronary arteries disease (CAD) increases mortality for cardiovascular disease, but patients with no evidence of heart disease have an excellent two years prognosis. Among LBBB patients, the non-invasive diagnostic investigations (ECG exercise test, echocardiography or radionuclide myocardial scintigraphy) show low specificity in excluding patients with CAD, compared to coronary artery angiography.
Aim: To compare myocardial perfusion obtained with myocardial contrast echocardiography (MCE) or myocardial scintigraphy in LBBB patients with normal or diseased coronary arteries at angiography and anteroseptal myocardial infarction (MI).
Methods: We consecutively studied 30 unselected LBBB patients (mean age 56 ± 8 years) and normal coronary arteries (15 patients) or anteroseptal chronic MI and left anterior descending CAD (>70% stenosis) (15 patients) at coronary angiography. All patients underwent MCE for assessment of myocardial perfusion (intermittent harmonic power Doppler with intravenous Levovist) and performed 99mTc-Tetrosfosmin SPECT scintigraphy.
Results: Among the 15 pts with LBBB and normal coronary arteries, MCE showed normal perfusion in 14 pts and impaired septal perfusion in 1pt, while in this same group, scintigraphy showed impaired septal perfusion in 14 pts and normal perfusion in 1 pt (MCE specificity 93.3% vs scintigraphy 6.6%). Among the 15 pts with LBBB MI and CAD, the two techniques significantly discriminated myocardial perfusion in distal septum (concordance rate 73.3%), posterior (73.3%), lateral (73.3%) and anterior wall (80% anterobasal; 86.6% mid-anterior; 80% distal-anterior). Conversely, there was a low concordance in the basal (33.3%) and midventricular septum (66.6%), with high accuracy of MCE. Comparing both groups of pts, rate of concordance significantly decreased, particularly in septal evaluation. Thus the two techniques significantly discriminated anterior wall and distal segments of inferior and lateral wall (83.3%), while scintigraphy poorly evaluated basal septum (16.6%), mid septum (33.3%) and distal septum (33.3%).
Conclusion: In pts with LBBB, myocardial scintigraphy is less accurate than MCE, showing a low specificity on patients with normal coronary arteries and a low accuracy in patients with MI and CAD.

INTERVENTIONAL CARDIOLOGY

P2865 High 2.5 year mortality among patients with "normal" angiograms: the ACRE study

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Background: Mortality among patients with normal angiograms is thought to be low (e.g. less than <1% per year). However this assumption is based on studies of patients undergoing angiography in the 1970s and 1980s.
Ojective: To determine the contemporary survival experience of patients with normal coronary arteries.
Design: prospective cohort study with 2.5 years follow up.
Setting: London Chest and St Bartholomews Hospitals, London, UK.
Patients: 4020 consecutive patients undergoing coronary angiography in 1996-7, recruited without exclusion criteria as part of the Appropriateness of Coronary Revascularisation (ACRE) study. The number of diseased vessels was defined as 0 (normal) in the absence of any narrowing in any of the 27 arterial segments defined in the Coronary Artery Surgery Study, < 1 in the presence of <75% narrowing, and 1 + in the presence of >=75% narrowing, or >0 50% in the left main stem.
Main outcome measures: all cause and coronary mortality (follow up complete in >99%, n=344 deaths).
Results: 19.4% of patients had 0, 10.0% <1 and 70.7% 1+ diseased vessels. Patients with 1+ diseased vessel compared with those with 0 had a higher age adjusted hazard ratio for coronary mortality (hazard ratio 4.52, 95% confidence interval 2.22-9.22). The crude risk of death from any cause at 2.5 years was 10.2% among patients with at least one diseased vessel and 6.5% among patients with normal coronary arteries. The mortality among patients with normal coronary arteries was more than twice that expected among the age and sex matched general population of England and Wales (3.1%).
Conclusion: In this contemporary study, patients with a normal angiogram had a mortality more than twice that of the age – sex matched general population. Reasons for this high mortality require elucidation.

P2866 Effect of direct stenting on outcome in patients treated with percutaneous coronary intervention on saphenous vein graft

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Objectives: We sought to determine whether direct stenting (DS) defined as stenting without pre-dilatation might prevent CK-elevation and the major adverse cardiac events associated with percutaneous coronary intervention (PCI) in saphenous vein graft (SVG) and to compare it with conventional stenting (CS) defined as stent implantation following balloon pre-dilatation.
BACKGROUD: Angioplasty of SVG is associated with frequent post-procedural enzyme elevation and late cardiac events. Therefore, evolving strategies are attempted to improve outcomes in SVG angioplasty.
Methods: From January 1994 to June 2001, 527 patients have been treated with PCI and stent implantation for SVG stenosis. One hundred and seventy patients with 229 lesions were treated with DS and 357 patients with 443 lesions were treated with CS without debulking. The study end-points included in-hospital and six months follow-up events.
Results: Baseline clinical and post-procedural angiographic characteristics were similar between the two groups. In the DS group, the prevalence of thrombus containing lesions before the procedure was greater (25.9% vs. 19.3%, p=0.047). The maximum CK-MB elevation post-procedure (9.5 ± 18.1 vs. 19.6 ± 47.8 mg/dL, p <0.001), CK-MB elevation more than four times the upper normal value (13.6 vs 23%, p = 0.012) and non Q wave Myocardial Infarction (MI) (10.7 vs. 18.4%, p = 0.024) were smaller in the DS group. Multivariate analysis showed that unstable angina was associated with non Q wave MI (odds ratio [OR] = 1.8; confidence interval [CI], 1.1 to 3.2, p = 0.03) and DS was inversely associated with Q wave MI (OR= 0.65; CI, 0.41 to 0.88; p = 0.04).
At six months, the TLR-MACE (including target lesion revascularization, death and Q wave MI) was significantly lower in the DS group (13.8% vs. 25.4%; p = 0.004). Multivariate analysis showed that DS (OR = 0.46; CI 0.27 to 0.77, p = 0.003) and diabetes (OR 1.62; CI 1.05 to 2.51, p = 0.03) were predictors of TLR-MACE.
Conclusions: Since DS decreased the enzyme release following PCI and reduced the TLR-MACE at six months, when technically feasible, DS should be considered as a viable option for treatment of SVG narrowing.

P2867 Direct coronary stenting (DS) compared to stenting after PRE dilatation (PRE) yields similar in-hospital outcome at lower costs

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Current stent delivery systems make direct stenting (stenting without predilatation) possible, but few controlled trials have been performed to evaluate the success, safety and cost-effectiveness. We conducted in a single center, a large prospective randomized clinical trial using the Medtronic AVE S670 stent to investigate whether on balance direct stenting (DS) has advantages over stenting with predilatation (PRE).
Four-hundred eligible patients undergoing elective coronary interventions were randomized either to DS (n=200) or to PRE (n=200). Treatment groups were similar regarding to demographics, anginal class, risk factors and lesion characteristics. Left anterior descending artery was in 40.3% involved. Lesion class B2/ C existed in 33%. Primary access was attempted in 94.5% via the transradial route with a successful radialis puncture of 91.5%.
Direct stenting was successful in 88.3% of cases. The failed direct stented lesions crossed over and were stented after predilatation resulting in an overall procedural success of 97.9%. Direct stenting did result in a similar acute angiographic result without increased complications. The rate of oversizing of the stent length was similar between DS (1: 1.64 mm) and PRE (1: 1.67 mm) as lesion length and stent length did not differ between groups. There was a trend of 4% more dissections occurring after initial stent placement in DS. Troponine I rise of more than 0.15 μg/L, used as a measure of distal embolization, was similar in both groups (DS: 17.8% vs. PRE: 17.1%). In-hospital major adverse cardiac events (MACE) of 3.0% and 30 days MACE of 2.6% were equal in both groups. There were modest savings in fluoroscopy time, contrast usage, and a reduction in angioplasty balloon usage (0.4 vs. 1.17 balloons/ patient; p <0.001). Although more stents were used in the PRE group there remained a cost saving of 190 Euro/ patient (p=0.02) in favor of direct stenting.
In conclusion, the AVE S670 stent showed excellent overall performance. DS in selected lesions is a safe and feasible but more demanding technique requiring experienced operators. DS does not lead to longer stent usage. Neither does it result in fewer dissections or distal embolizations. Although DS is highly successful with similar in-hospital outcome it yielded only modest cost-savings if compared to PRE.

P2868 Effect of balloon oversizing in stenting small vessels

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The aim of present study was to evaluate whether the placement of coronary stents using 3.0 mm balloon size in the vessels with the reference diameter <=2.8 mm favorable affects clinical and angiographic outcome.
Methods: Data from 509 consecutive patients with 610 lesions, with the reference diameter <=2.8 mm determined by QCA, in whom stent was implanted were analyzed. According to final balloon diameter two groups were created, Group I (124 pts) - with the balloon size < 3.0 mm and Group II (385 pts) - with the balloon size 3.0 mm. Two groups were comparable for clinical and procedural characteristics, as well as the incidence of complex lesions (58.9% vs. 65.2%, p = ns). The reference vessel size was 2.15±0.33 mm and 2.43±0.29 mm (p<0.01), the balloon-artery ratio 1.19±0.2 and 1.25±0.16 (p<0.002) in Groups I and II, respectively. Clinical follow-up was obtained for all patients after 12±9 months. All patients had angiographic follow-up after 6±4 months by protocol.
Results: Two groups had similar incidence of in-hospital complications (non-Q-MI 4.0% vs. 3.7%, and Q-MI 1.6% vs. 2.9%, p = ns for both). There were no in-hospital CABG or deaths. Two patients in both groups (1.6% vs. 0.5%) had acute stent thrombosis, whereas subacute stent thrombosis occurred in 3 patients (2.4%) in Group I, and in 1 patient (0.3%) in Group II, p = ns. Long term outcome: Recurrence of angina was similar in two groups (26.6% vs. 25.5%, p = ns). Long-term MACE (myocardial infarction, CABG and deaths) were not different in two groups (8.8% vs. 7.8%, p = ns). Angiographic restenosis rate was 41.1% in group I and 37.4% in group II, p = ns. Target lesion revascularization rate (TLR) was 35.5% in group I and 37.4% in group II, p = ns, and target vessel revascularization rate (TVR) was 41.9% in group I and 40.8% in group II, p = ns.
Conclusions: Despite the presence of more favorable baseline characteristics due to a larger reference vessel size, balloon oversizing in small vessel stenting does not seem to lower the incidence of angiographic restenosis or to improve clinical outcome.

P2869 Are distal protection devices required for PTCA of instent restenosis in degenerated saphenous vein grafts?

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Background: Coronary slow flow/no reflow may occur after percutaneous coronary interventions (PCI) in degenerated saphenous vein grafts (SVG). Distal protection devices have been shown to reduce the incidence of slow flow/no reflow in PCI of degenerated SVGs in de novo lesions. It is unclear whether PCI of in-stent restenosis of degenerated SVGs is associated with slow flow/no reflow.
Methods: Between 2000 and 2001, 54 consecutive patients with instent restenosis of degenerated SVGs underwent PCI without distal protection at the Lenox Hill Hospital Heart and Vascular Institute. Procedural and in-hospital outcomes were examined.
Results: The average age was 68.1 ± 10.4 years and 27.8% of the patients were diabetic. The procedural characteristics and results are shown in the table below.

Characteristic	Results
Angiographic Success	98.1% (53/54)
Lesion Length	13.5 ± 6.4 mm
Cutting Balloon Used	46.3% (25/54)
New Stent Implanted	46.3% (25/54)
Rotational Atherectomy Used	0.0% (0/54)
Gamma Brachytherapy	18.5% (10/54)
Episode Slow Flow/ No Reflow	0.0% (0/54)
Death	1.9% (1/54)
Myocardial Infarction (Q and Non Q wave)	0.0% (0/54)

Results

Conclusions: In this consecutive series of patients with instent restenosis of degenerated SVGs undergoing PCI without distal protection there were no episodes of slow flow/no reflow and no procedure related myocardial infarction. It would appear that distal protection devices may not be necessary for PCI of instent restenosis in degenerated SVGs.

P2870 Safety and efficacy of Angioguard protection device for prevention of distal embolization during percutaneous coronary intervention in patients with unstable angina

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The use of IIbIIIa receptor blockers decreases the number of major adverse cardiac events during PCI. However, microinfarcts (post procedural CK-MB elevations) occur despite optimal antithrombotic treatment. In patients (pts) with increased risk of atheroembolization during PCI the use of additional mechanical protection of embolization could be considered.
The purpose of the study was to determine safety and efficacy of additional use of first generation Angioguard (coronary filter) for prevention of microembolization during PCI in pts with unstable angina (UA).
Methods: 31 pts with UA (Braunwald IIB, IIIB) undergoing urgent coronary angioplasty (PCI) with stenting, were randomized in the cath lab for additional use of Angioguard coronary filter. All pts were treated with aspirin, ticlopidine (500 mg/d), heparin (60U/kg, ACT 200-300sec.) and eptifibatide (bolus 2x 180ug/kg i.v. and 2ug/kg/min. infusion for 18-24h). We analyzed the extend of microembolization (serial CK-MB) and presence of embolic material in the device after procedure. We also assessed the frequency of technical problems and major cardiac events (death, myocardial infarction (MI), urgent target vessel revascularization (TVR)).
Results: PCI was successful in all pts. There was no death, Q wave MI or urgent TVR. Angioguard was successfully installed in 100% pts, however balloon predilatation was necessary in 9(60%) pts. In 9 pts (60%) there was no possibility to prevent big side branches originated closely to the culprit lesion. Presence of embolic material in the filter was confirmed in microscopic analysis of each device. However maximum CK-MB level was 34±10 U/L in Angioguard goup vs 9±5U/L in the group without protection device.
We conclude that first generation Angioguard protection device does not successfully prevent distal embolisation during PCI in pts with UA and its use is associated with many number of technical problems.

P2871 Initial experience with a new concept 8 French compatible directional coronary atherectomy catheter: in-hospital and 30-day clinical outcome

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Background: The Fox Hollow (FHT, Fox Hollow Technologies Inc.,Redwood City,CA) is a new atherectomy device designed for more efficient and easy plaque removal. Device is compatible with a large lumen 8 French guiding catheters and has a 4mm long cutting window which allows negotiation in complex anatomy. The FHT catheter does not need an urging balloon to establish vessel wall contact and can be advanced over routine PTCA wire as a monorail device.
Methods and Results: To assess safety and efficacy, the FHT catheter was utilized in 30 lesions in 24 patients (mean age 59±14 years; diabetes mellitus 21%; unstable angina 25%, prior CABG 29%). 87% of lesions were B2 or C type, 27% were in-stent restenosis and 57% of lesions were located in mid or distal part of coronary artery. Mean reference vessel diameter was 2.71±0.65 mm and mean lesion length was 11.4±7.1 mm. Successful atherectomy with tissue retrieval was performed in 29 lesions (96.7%). One calcified lesion could not be crossed with the device.
Atherectomy alone was utilized to treat 4 lesions and adjunctive treatment was performed in 26 (87%) lesions (stenting in 23 and POBA in 3). Following atherectomy mean diameter stenosis was reduced from 66% to 28% and further to 11% following adjunctive treatment. Acute gain was 1.9±0.9 mm. In one lesion adventitial staining was observed following atherectomy and was successfully treated with stent implantation. Four patients (16.7%) had in-hospital non-Q-wave myocardial infarction (MI). No deaths, Q-wave MI and repeat revascularization (percutaneous or CABG) occurred in-hospital and at 30-day follow-up. Six-month angiographic follow-up is scheduled for all patients.
Conclusion: Plaque debulking with the FHT catheter can be performed safely and effectively in the relatively small vessels and lesions located in mid-distal artery segment. A larger case series with 6-month clinical and angiographic follow-up will be available at the time of presentation.

P2872 Reduced wall stretch after DCA and stent deployment: a serial intravascular ultrasound evaluation of the mechanisms of lumen enlargement

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Background: Stenting preceded by directional coronary atherectomy (DCA) reduces the occurrence of in stent restenosis. The aim of the study was to compare the mechanism of lumen enlargement after stenting preceded by DCA with predilatated stenting using intravascular ultrasound (IVUS) assessment.
Methods: 20 patients treated with DCA followed by stenting (Gr 1) were compared with a second group of 30 patients who underwent stenting after balloon angioplasty (Gr 2) The two groups were similar, regarding demographic, clinical, angiographic and ultrasonographic characteristics. Serial IVUS studies, pre-intervention, and post-stenting were performed. External elastic membrane (EEM), lumen, and plaque cross-sectional area were measured at 1-mm intervals through the entire stent length and in the proximal and distal reference segments (5 mm from the stent edge).
Results: There were no differences in clinical, angiographic, IVUS and procedural characteristics between the 2 groups. The increase in mean EEM area was significantly smaller in Gr1 than in Gr2 (3,05±0,8 mm^2 vs 4,28±1,98 mm^2 respectively, $p<0,001$). The increase in lumen area was slightly greater in group 1, although the difference was not statistically significant (7,10±2,23 mm^2 vs 6,31±3,42 mm^2; respectively, p=NS). Axial plaque shift into the reference segments was significantly reduced with the DCA use (0,77±0,55 mm^2 vs 1,55±0,94 mm^2 respectively, $p<0,01$).
Conclusion: Plaque removal by means of DCA followed by stent deployment reduces vessel stretch and plaque shift into reference segments as compared to stenting with predilatation.

P2873 Serial Lumen dynamics after Debulk-stenting assessed by intracoronary ultrasound: comparison with optimal lesion debulking

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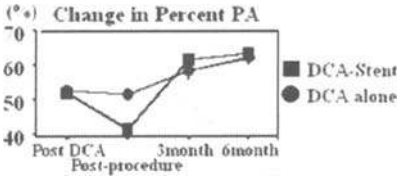
This study aim was to compare the lumen dynamics after debulk-stenting assessed by serial intracoronary ultrasound (ICUS) examinations with debulking alone. After optimal ICUS guided directional coronary atherectomy (DCA), 117 lesions were randomly assigned to the DCA-stent group (n=58) or DCA alone group (n=59). Multilink stent(s) was implanted in the DCA-stent group. Follow-up ICUS were performed 3 and 6 months after the procedure. Eligible serial IVUS images were obtained in 83 lesions (DCA-stent: 42, DCA alone: 41). Vessel and lumen area were measured, and plaque area and percent plaque area were calculated. Results are shown in the table and figure.

Serial Lumen Dynamics

	Post LA	d1PA	d1VA	3MFu LA	d2 PA	d2 VA	6MFu LA
DCA-stent	10.2±1.7	4.1±2.0	1.1±2.2	7.2±1.9	-0.1±1.7	-0.7±1.8	6.6±1.7
DCA alone	8.7±2.2	1.3±2.5	0.4±3.0	7.8±3.1	0.2±1.4	-0.7±1.8	6.9±3.1
P value	0.0006	<0.0001	NS	NS	NS	NS	NS

LA = lumen area (mm^2), PA = plaque area (mm^2), VA = vessel area (mm^2), MFu = month follow-up, d1 = 3MFu - post, d2 = 6MFu - 3MFu.



Change in percent plaque area.

Conclusion: Neointimal proliferation after DCA-stenting almost finishes until 3 month follow-up associated with compensatory vascular remodeling as well as DCA alone. However, neointimal proliferation after DCA-stenting is so exaggerated that the bigger immediate lumen gain by additional stenting may be cancelled during the follow-up period.

P2874 First clinical experience with the FX minirail catheter: a novel device for the enhancement of percutaneous coronary intervention in de novo and restenostic lesions

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Background: Complex lesion morphology requiring high pressure balloon dilation and instent restenosis remain two scenarios that continue to challenge conventional angioplasty balloons. Application of high pressure can result in increased arterial trauma and major dissections. Balloon slip in instent lesions often results in significant extension of injury. We report on the first clinical experience with a new angioplasty device designed to effect vessel dilation with a precise and low-pressure inflation in both de novo and restenostic lesions. The FX minirail catheter has an integral wire positioned external to a dilating balloon and a short 12mm guidewire lumen distal to the balloon. Upon balloon inflations both wires, being external to the balloon, prevent slippage and introduce high focal stresses longitudinally along the wire length at low inflation pressures.
Methods: A registry study was performed on de novo and restenostic lesions using a staged inflation protocol to assess the stenosis resolution pressure of the lesions with this device as well as its safety and efficacy.
Results: Thirty patients (26 males) undergoing PCI for coronary stenoses were included. They had a mean age of 60.9±11.9 years with the following risk factor profile: smokers 15, hypertension 17, hyperlipidemia 13, family history 10. A total of 37 lesions (25 de novo, 12 instent restenosis) were treated with a mean reference vessel diameter of 2.73±0.49mm, mean stenosis of 77.5±9.5% and mean lesion length of 11.76±4.58mm. The FX, used as the primary balloon, successfully crossed and dilated 100% of the lesions leaving a mean residual stenosis of 26.9±13.3%. The mean stenosis resolution pressure was 4.5±2.9 atm, and no balloon slippage was observed. Eight dissections (type A-2, type B-6) were observed. In 51.5% of lesions a stent was deployed resulting in a final residual stenosis of 15.3±13.1% with a single residual (B) dissection. In hospital MACE was 0. At two week follow-up there remains MACE of 0.
Conclusion: FX minirail design in this initial registry trial appears to provide for a safe and effective low-pressure angioplasty technique in de novo and restenotic lesions.

P2875 Euro-SPAH: a European trial on the anti-restenotic effect of Intravascular Sonotherapy (IST) after multi-vessel stenting of de novo lesions

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Background: Animal studies have shown that IST inhibits smooth muscle cell proliferation and reduces intimal hyperplasia, % stenosis and mean neo-intimal thickness. The SILENT registry (110 pts) demonstrated that IST is both safe and feasible to prevent coronary restenosis (at 9 mths). Euro-SPAH is a multicenter, double-blind, randomized trial investigating the efficacy of IST to reduce the rate of restenosis after multi-vessel, direct stenting of de novo lesions using the BX™ Velocity™ stent. Efficacy will be measured as angiographic late lumen loss at 6 months post-procedure. Safety will be assessed at 1, 6 and 12 months.
Method: Patients receiving de novo stents in native coronary arteries are randomized to receive either sham treatment (non-activated sonotherapy) or IST. The sample size has a 90% power to detect a late loss (LL) difference of 0.21mm between the sham group (expected LL 0.84mm) and IST group (expected LL 0.63mm) as assessed by off-line QCA at 6 months (primary endpoint). The secondary endpoints are short and long-term safety from MACE (1, 6, 12 mths), neo-intimal hyperplasia from IVUS (6 mths), and late thrombotic occlusion (1 mth). Inclusion criteria: patients with stable or unstable angina (Braunwald 1-3, B-C) or documented silent ischemia with one or more successfully stented de novo or non-stent restenotic lesions at least 2.5mm in diameter and up to 35mm in length.
Results: Between October 2000 and January 2002, 403 patients (1.2 lesions/pt) were randomized to sham or IST at 23 sites in Europe. Approximately 95% of the patients were successfully treated with sham or IST (inability to cross the stented lesion with the study catheter: 14 pts, failure of the catheter or instrument: 23 pts). Preliminary baseline characteristics: age 61.9 yrs, male 78.9%, UAP 29.7%, stable angina 57.2%, silent ischemia 12.8%, previous MI 43.1%, previous revascularization 18.7%, diabetes 17.4%, hypercholesterolemia 81.0%, current smoker 28.6%. Vessels: LAD 40.5%, RCA 37.1%, LCX 22.4%. Before treatment, the mean vessel size was 2.88mm with an MLD of 1.00 mm and a lesion length of 12.37mm. The mean reference diameter post-procedure was 3.01mm with an MLD of 2.49mm, resulting in a diameter stenosis of 17%. The mean stent length per lesion was 16.9mm. MACE up to 30 days: death 0.25%, QMI 0%, non-QMI 3.5%, CABG 0%, target lesion re-PTCA 0%, non-target vessel re-PTCA 0.5%, (sub-)acute occlusion 0.75%.
Conclusion: The primary and secondary endpoint results at 1 and 6 months will be presented at the meeting.

P2876 Cutting balloon angioplasty versus balloon angioplasty for treating diffuse in-stent restenosis

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Background: Cutting balloon angioplasty (CBA) has been reported to decrease restenosis rates compared to balloon angioplasty (POBA) in the treatment of focal in-stent restenosis (ISR). The aim of this study was to compare the clinical and angiographic outcomes of CBA compared to POBA in diffuse ISR.
Methods: Consecutive patients with diffuse ISR lesions (lesion length>=10mm or total occlusions) treated with CBA or POBA in our institution between May 1994 and June 2001 were included in this analysis. Lesions at vessels treated with intracoronary brachytherapy or radioactive stents in previous interventions were excluded. Major adverse cardiac events (MACE) were defined as death, myocardial infarction and target lesion revascularization (TLR).
Results: In total 161 lesions treated with CBA and 114 treated with POBA were included. There were no significant differences regarding clinical and angiographic characteristics between the 2 groups. A larger balloon-to-artery ratio was used in the lesions treated with CBA resulting in greater acute lumen gain (table).

	CBA	POBA	
Mean reference, mm	2.69±0.5	2.70±0.5	p=0.91
MLD pre, mm	0.88±0.4	0.97±0.4	p=0.06
Lesion length, mm	16.78±5.5	17.15±6.8	p=0.62
MLD post, mm	2.34±0.5	2.21±0.6	p=0.62
Balloon/artery ratio	1.26±0.2	1.17±0.2	p=0.02
Acute Gain, mm	1.46±0.6	1.26±0.6	p<0.01
Restenosis, n (%)	48 (37,8)	20 (31,7)	p=0.52
TLR at 12 months, n (%)	27 (16.8)	13 (12)	p=0.30
MACE at 12 months, n (%)	33 (20.5)	19 (17.6)	p=0.64

MLD: minimal lumen diameter

During the clinical follow-up period (14.2±10.2 months) there was no difference in angiographic restenosis rate, TLR and MACE rates between the 2 groups. The main limitation of this study stands in a different rate of angiographic follow-up between the two groups (79.9% for CBA and 57.3% for POBA).
Conclusions: CBA has similar clinical and angiographic results with POBA in the treatment of diffuse ISR. Different rates of angiographic follow-up could have affected the propensity to perform TLR.

P2877 A little shorter stents than the culprit length reduce restenosis surrounding stents

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It was reported that drug-coated stent reduced restenosis in Europe.But we can not use these stents in Japan, therefore it is necessary to purchase conventional and convinient method for the prevention of restenosis. Objective: We examined whether it contributed to the reduction of restenosis surrounding stents to use a little shorter stent than the culprit lesion length or not. Methods: Ninety-six type A lesions of 96 patients had stenotic (> 75% visual stenosis) lesion length around 10mm. 47 and 49 patients of them were revascularized at random using NIR stents with 9mm length (S group) and 12mm length (L group), respectively. Minimal luminal diameter (MLD), stent-proximal diameter (SPD) and stent-distal diameter (SDD) obtained by QCA, of two groups were compared at post-procedure and 6 months. Results: There was no significant difference in gender, age, distribution of coronary risk factors and culprit lesions, lesion length, pre-reference diameter, pre-MLD, stent-proximal and distal diameter of two groups at post-procedure. Restenosis occurred in 8 (16%) and 1 (2%) patient of L and S group, respectively ($p<0.01$). All restenosis of L group were observed surrounding stent-distal site. There was no difference in SPD of two groups at 6 months. Six-month MLD (1.56 ± 0.23 vs. 2.23 ± 0.33 mm, $p<0.01$) and 6-month SDD (1.88 ± 0.42 vs. 2.46 ± 0.50 mm, $p<0.01$) of L group were significantly less than those of S group. Conclusions: It may cause increase in restenosis of L group that the mismatch between distal diameter of stent and distal vessel diameter of the culprit tends to occur, when a little longer stent than the stenotic lesion length is used. A little shorter stent than the stenotic lesion length may have to be used to prevent restenosis especially surrounding stent-distal site. Using short stent may be one of convenient methods for prevention of restenosis in Japan, where drug-coated stent is unable to be used. μ

P2878 Determinants of the expansion of different coronary stents in curved stenotic lesions: an in-vitro experimental study

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Background: Coronary stent implantation in angulated vessels is a challenging issue, as there is currently lack of consensus regarding the type and length of stents best suitable for such lesions.
Aim of this study was to assess comparatively the expansion parameters of several new generation stent types in a curved stenotic phantom.
Methods: Identical silicon models of 3.2 mm diameter with a 55% concentric elastic stenosis were industrially manufactured. A number of 5 stents for each length and type (AVE [Medtronic] 3.5/12, 3.5/18 mm; Penta [Guidant] 3.5/13, 3.5/18 mm; BX-Sonic [Cordis] 3.5/13, 3.5/18 mm; FlexMaster [Jomed] 3.5/12, 3.5/16 mm) were implanted in the stenotic models using appropriate balloon pressures to achieve a full stent expansion. The forces exerted during balloon inflation (Finfl) and after balloon deflation (Fstent) were continuously registered at a rate of 20 measurements per second using a high sensitive dynamometer placed externally on the model wall. The minimal (MLD) and reference luminal diameter (RLD) of the stents and respectivelly of the inflated balloons (BDmin, BDref) were determined by X-ray imaging with direct magnification.
Results: All stents presented a good wall apposition without deformation of the phantom curvature. No significant differences of the expansion parameters related to the stent length were found. The displacement forces on the vessel wall (higher for AVE and Penta) were within a low range for all stents. Expansion parameters are summarized in the table (mean ± SD).

Parameters of stent expansion

Stent (n=10)	Inflation pressure	MLD (mm)	RLD (mm)	BDmin (mm)	BDref (mm)	%Recoil	Finfl (mN)	Fstent (mN)
AVE	10 bar	3.05 ±0.19	3.75 ±0.13	3.69 ±0.05	3.79 ±0.03	17 ±4	133 ±41	34 ±15
Penta	11 bar	2.94 ±0.18	3.78 ±0.07	3.70 ±0.04	3.80 ±0.05	21 ±5	125 ±30	23 ±14
BX-Sonic	12 bar	2.68 ±0.10*°	3.47 ±0.06*°	3.48 ±0.07*°	3.59 ±0.06*°	23 ±3*	113 ±22	13 ±7*
FlexMaster	12 bar	2.53 ±0.08*°	3.28 ±0.05*°"	3.39 ±0.02*°"	3.56 ±0.04*°	25 ±2*	58 ±16*°"	9 ±7*

%Recoil = 100*(1-MLD/BDmin). *p < 0.05 compared to AVE; °p < 0.05 compared to Penta; "p < 0.05 compared to BX-Sonic.

Conclusions: In this curved elastic stenotic model AVE stents showed the lowest recoil and reached together with Penta stents the largest MLD, while FlexMaster developed the lowest expansion forces and presented together with BX-Sonic stents significant lower MLD values.

P2879 High success rate in recanalization of chronic total coronary occlusions with a novel guidewire principle using the guidance of micro channels

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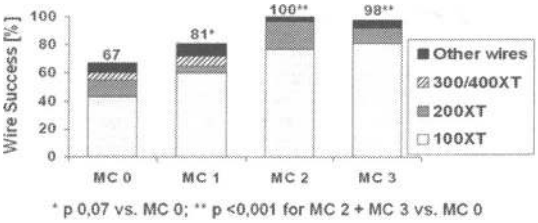
Background: Vascular micro channels (MC) in chronic total coronary occlusions (CTO) may guide recanalization wires and improve success rates. The new ACS Cross-IT®XT guidewire family has distal tip tapering from 0.014" to 0.010" that eases entrance into MC. Tip stiffness increases gradually from the 100XT-wire to the 400XT-wire.
Methods: We included 204 consecutive pts. with 214 CTO. Age of occlusion was >3 months to 20 years and occlusion length 24.1(5-80)mm. MC as visible on cineangiography were none in 37% (MC 0), incomplete in 26% (MC 1), complete in 14% (MC 2) and complete with distal capillary refill in 23% (MC 3). In all lesions the first attempt was done with the 100XT-wire trying carefully to follow MC. If necessary tip stiffness was stepwise increased to the 400XT-wire.
Results: Success rates for crossing the occlusion were 61% for the 100XT-wire, 76% for all Cross-IT®XT wires and 82% including other additional wire types. Wire success was dependent on visibility and completeness of MC (Figure 1). If MC were visible 60% to 81% of occlusions could be passed with the 100XT-wire. Vessel success rate was 79%. In-hospital events were pericardial tamponade in 0.5%, non-q wave myocardial infarction in 1%; no pt. died.
Conclusions: The use of a new guidewire family with a tapered tip and the concept of stepwise increase of wire tip stiffness is safe and very effective in recanalizations of CTO. Wire success was significantly dependent on the visibility of MC.



* p 0,07 vs. MC 0; ** p <0,001 for MC 2 + MC 3 vs. MC 0

P2880 Five F VS 6F transradial coronary intervention randomised study: no technical advantages for the 5F

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Background: Smaller guiding catheters (GC) may have some advantages in patients (pts) with small coronary arteries and with transradial (TRA) interventions. However, their efficacy and safety are yet to be demonstrated. We performed a prospective randomised dual centre study to compare a new 0.058" lumen 5F GC vs standard 6F GC in TRA routine PTCA.
Method: All pts eligible were randomised between the 5F vs 6F GC group before the PTCA. Primary end-point was procedural success defined as a procedure performed via the TRA route, done with the randomised GC, adequate stent delivery when needed, residual stenosis of less than 30%, and final TIMI 3 flow. Secondary end-points were also collected.
Results: A total of 216 pts were randomised. Mean age was 64 yrs and there were 81% men. There were no clinical baseline characteristic differences between the groups. Clinical indications for PTCA were stable angina (46% vs 41%; 6F vs 5F), unstable angina (23% vs 29%), post-MI (14% vs 16%), and silent ischemia (17% vs 14%). A mean of 1.5 and 1.4 vessels/pt (6F vs 5F) were dilated. Stents were used in >85% in both groups. There were no differences in stent size (3.0± 0.4 vs 3.0± 0.5;6F vs 5F),length (15.0± 7.3 vs 15.1± 8.5) and direct stenting attempt(71% vs 62%) between the groups. Direct stenting success was achieved in 95% in both groups. Two stents were lost in the 5F vs 0 in the 6F group (p=ns). Mean procedural time, fluoroscopic time, and quantity of contrast used during the procedures were similar between the groups. The number of GC used was also similar (1.3± 0.5 vs 1.4± 0.8; 6F vs 5F). There was one RCA ostium dissection in the 5F group. No other complications occurred. Transfemoral crossover occurred in less than 1% in both groups. Crossover to 5F occurred in 0.9% of the 6F group, because of a small radial artery. Six F crossover occurred in 6.8% of the 5F group (p= 0.05), because of backup insufficiency, GC kinking, or need for a larger stent (5.0mm). Procedural success was obtained in 93% of the 6F group vs 90% of the 5F group, and intention to treat success in 95% vs 97% (p=ns).
Conclusions: Transradial routine PTCA using 5F GC is safe, but necessitates crossover to a 6F GC in 6.8% of the cases, and offers no clear advantages over the 6F GC. It may have potential benefits in pts with small radial arteries.

P2881 NUGGET trial (NIR Ultimate Gold-Gilded Equivalancy Trial): 6 month IVUS follow-up

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The NUGGET trial was a prospective, multicentre randomised trial comparing the stainless steel NIR PRIMO stent, with a gold-coated NIROYAL stent. The primary objective of the trial was to demonstrate equivalency of the minimal lumen diameter (MLD) at sixth month angiographic follow-up. Secondary objectives included percentage plaque obstruction measured by intravascular ultrasound (IVUS) at 6 months. 603 pts were randomised, of which 111 pts were enrolled in an IVUS substudy which is the subject of this report. Stents were interrogated with the CVIS UltraCross system using a motorized pullback and analysed in an IVUS core laboratory. 6 month IVUS measurements were available on 105 of this subgroup (95%). Mean stent area was similar in the two groups (steel 8.00 ± 1.99 mm^2, gold 7.86 ± 2.24 mm^2). Lumen volume within the stented segment was significantly reduced in the NIROYAL compared with the NIR PRIMO group (steel 99.21 ± 56.42 mm^3, gold 72.87 ± 38.31 mm^3, difference 26.34 mm^3, CI 8.11, 44.56), as was MLD (steel 2.15 ± 0.57 mm, gold 1.92 ± 0.58 mm, difference 0.23 mm, CI 0.01, 0.45). Mean area of neointimal hyperplasia was significantly higher in the NIROYAL group (steel 1.99 ± 1.29 mm, gold 2.37 ± 1.32 mm, difference 0.73 mm, CI 1.22, 0.25). As a consequence, the volume of in-stent obstruction was significantly higher in the NIROYALä group (steel 25.9 ± 16.8%, gold 36.7 ± 18.7%, difference 10.8%, CI 17.5, 4.0).
Thus, the gold-coated NIROYAL is associated with significantly more intimal hyperplasia and instent restenosis than the stainless steel NIR PRIMO stent when investigated by IVUS six months after stent implantation. In this study, these adverse changes documented by IVUS were not associated with an increase in major adverse cardiac events (MACE).

P2882 Low pressure inflation by the GuardWire embolisation protection device causes no harm in native coronary arteries: an angiographic follow-up

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Background: Low pressure inflation might cause adverse local effects during percutaneous coronary interventions (PCI) in native coronary arteries. The GuardWire (GW) embolisation protection device was recently introduced in the clinical arena but little is know about short- and long-term follow-up at the site of the temporary distal occlusion balloon.
Methods: By quantitative coronary angiography (QCA) we analysed the vascular segment after final deflation of the GW distal protection balloon (day 1) and compared the identical region in the first 50 patients (pts; mean age 60±12 years, 12 women; left anterior descending: n=26, right coronary artery: n=20, and left circumflex: n=4) that had recatheterisation (day 2) at our institution. Cumulated inflation time, number of inflations and maximal size of the distal balloon were included in the analysis.
Results: Pts were restudied 120±125 days (range 1 to 426 days) after PCI because of reinfarction (n=8) or infarction (n=2), acute coronary syndrome (n = 14), elective study (n = 14), or for other reasons (n=12). Acutely the temporary low pressure inflation balloon did not induce any local changes on day 1 in any patient. Similarly, on day 2 there were no changes and lumen diameter of the region of interest was identical (2.6±0.8 and 2.6±0.7 mm; ranges: 1.61 to 5.11 and 1.55 to 4.75 mm, respectively), and the GW did not cause any stenosis or remodeling. The number and time of inflations (cumulated: mean, 11.7±11.6 minutes; range, 2.1 to 59 minutes) and the size of the balloon did not have any adverse effects as well.
Conclusion: This preliminary follow-up angiographic study suggests that the low pressure temporary occlusion balloon does not cause any harm to the vascular bed at the site of the former inflation.

P2883 Noninvasive assessment of coronary artery stents. A comparison of multislice-CT-angiography and MR-angiography in a phantom study with 19 stents

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Purpose: Evaluation of the lumen visibility of several coronary artery stents by MS-CTA and MRA.
Material and Methods: Nineteen different coronary artery stents (materials steel, nitinol, tantalum) were implanted in plastic tubes (inner diameter 3mm). For MS-CTA (Kollimation 4x1 mm; tablefeed 2 mm/rotation, mAs 300, kV 120), the tubes were filled with nonionic contrast medium (200 HU), closed at both ends and positioned in a plastic container with oil (HU –70). For MRA, the tubes were integrated in a flow model, scans with and without flow (TSE-sequence) were obtained and subtracted. By this, only flow appeared signalintense.
Results: During MS-CTA, artifacts caused a complete lumen obscurity in the Wiktor, the Jograft and the Nir Royal stent. In all other products small parts of the lumen were visible (lumen narrowings of 62-94%). During MRA, the lumen was completely visible with high signal intensity in the Wiktor stent. The signal was moderately decreased in the Radius stent and severely to totally decreased in the other devices.
Conclusions: Although parts of the stentlumen were delineable with MS-CTA and/or MRA, a reliable assessment with detection of possible in-stent stenoses appears realistic only for the tantalum stent in MRA.

P2884 The impact of plasma levels of CRP on the restenosis rate after successful coronary stenting. Results from the GENERATION study

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Background High plasma C-reactive protein (CRP) levels, has been associated with an increased risk of short and long-term ischemic complications in patients with coronary artery disease. However, the impact of preprocedural plasma CRP levels on the angiographic restenosis rate after succesful coronary stenting (CS) has not been clarified yet. The purpose of this substudy was to evaluate this issue.
Methods The GENERATION study was designed to evaluate globally, the impact of several serum markets estimated upon admittance (CRP, Lpa, homocystein and seropositivity for chlamydial infection) on the long-term cardiovascular morbidity and mortality as well as on the restenosis rate after coronary stenting. For the purpose of this study a total of 483 consecutive patients who underwent successful CS due to stable or unstable coronary syndromes were recruited in a period of 28 months in our institute. Complete clinical follow up was obtained from 465 (96.3%) pts in a period of 3-years.
Results: By 1-year, 121 patients (121/465 24.1%) developed recurrence of symptoms. During this 1-year time period, 309 (309/465 66.5%) patients underwent angiographic restudy, including 114 (114/121 94.2%) symptomatic and 195 (195/344 55.1%) asymptomatic. Pts were classified into four groups A, B, C and D according to the quartiles of plasma CRP values. Angiographic restenosis (>50% in-stent lumen diameter stenosis) was observed in 108 (108/309 35%) pts. The distribution of restenosis among the quartiles of CRP are presented in the table. There was no statistically increased risk of in-stent restenosis with increasing of CRP tertiles (P=0.89)

A (0.5)	B (0.54)	C (0.64)	D (1.01)	P
32.1	33.8	37.3	36.6	0.89

Numbers are presented as %. Values in parentheses represent median CRP value for each quartile of CRP as mg/dl

Conclusions: The results of the GENERATION study suggest that high plasma levels of CRP are not related to the rate of restenosis after successful CS. More studies are needed to elucidate this issue.

P2885 Cytokines and inflammatory markers are released early after coronary stenting and are related to 6-month clinical outcomes

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Circulating levels of inflammatory markers, such as C-reactive protein (CRP) and proinflammatory cytokines have been reported to be present in patients (pts) with acute coronary syndromes and are related to unfavorable short-term outcome. The effect of coronary stenting on cytokines release and cell-mediated immunity is not well known. Purpose: To investigate the systemically detectable inflammatory response and immune system activation in pts undergoing coronary stent implantation. The study also investigates the relationship between inflammatory markers after stenting and major adverse cardiac events (MACE) at 6-month follow-up. Methods: We measured serum concentration of high-sensitivity CRP (hs-CRP), interleukin-6 (IL-6), interleukin-8 (IL-8)(as marker of inflammation)and serum soluble interleukin-2 receptor (sIL-2R) for T-lymphocytes activation(as a marker of cell-mediated immunity). Forty pts were enrolled to single vessel stent implantation in native coronary arteries. Peripheral venous blood samples were taken before stenting and 6 h, 48 h, and 12 weeks(wk) after the procedure. Pts were divided into 2 groups according to their 6-month follow-up: group 1: 6 pts with MACE, and group 2: 34 pts with uneventful course. Nonparametric tests were used; results are expressed as median. $P<0.05$ was significant. Results: The level of hs-CRP was 0.45 mg/dL before, 0.56 mg/dL at 6 h (P=NS) and 2.77 mg/dL at 48 h ($P<0.05$). At 12 wk, a decrease to 0.22 mg/dL was detected ($P<0.05$). IL-6 increased from 7.80 pg/mL to 11.00 pg/mL at 6 h ($P<0.05$), decreasing to 8.90 pg/mL at 48 h ($P<0.05$)and to 2.77 pg/mL at 12 wk ($P<0.05$). IL-8 increased from 6.30 pg/mL to 12.60 pg/mL at 6 h ($P<0.05$), decreasing to 7.30 pg/mL at 48 h ($P<0.05$) and to 6.90 pg/mL at 12 wk (P=NS). There was no change for sIL2-R level at 6 h (baseline: 420 vs 6 h: 430 U/mL;P=NS). sIL2-R increased to 476 U/mL at 48 h ($P<0.05$). There was also an increase in sIL2-R at 12 wk, with a peak value of 495 U/mL ($P<0.05$). When compared to pts with no clinical events, pts with MACE (group 1) presented significant increases in hs-CRP at 48 h (Group 1: 4.94 vs Group 2: 1.84 mg/dL; P=0.043) and IL-8 at 6 h (Group 1: 26.75 vs Group 2: 13.55 pg/mL; P=0.048), representing 2.7 and 2.0-fold increases, respectively. Conclusions: Proinflammatory cytokines and acute phase proteins are released into peripheral circulation early after coronary stenting. Cell-mediated immunity occurs early and at least after 12 wk after stenting. The occurrence of MACE at 6-month is associated with the magnitude of inflammation after the procedure.

P2886 Predictors of event free survival in patients treated for in-stent restenosis. Insight from the RIBS ramdomized trial

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Background: In-stent (ST) restenosis (RE) constitutes a clinical and technical challenge affecting a growing number of patients (P). Although satisfactory initial results are usually obtained with repeat percutaneous coronary interventions (PCI) the risk of recurrent RE remains high. There is, therefore, still a need to determine predictors of the long-term clinical outcome in these P.
Methods: The RIBS trial (Restenosis Intra-stent Balloon angioplasty vs elective Stenting) was a randomized study where these two strategies were compared in 450 P [224 allocated to ST and 226 to balloon angioplasty (BA)]. The recurrent RE rate was similar in both groups (38% in the ST arm vs 39% in the BA arm). However, in the pre-specified subgroup of P with large vessels (>3mm) RE rate was reduced in the ST arm (27% vs 49%, p=0.007). One-year follow-up (FU) was obtained in all 450 P (with no P lost to FU). Events assessed at FU included death, myocardial infarction (MI) and target vessel revascularization (TVR). By protocol, symptoms or objective evidence of ischemia was required for TVR.
Results: During 1-year FU 15 P died (8 ST arm, 7 BA arm), 19 suffered a MI (6 ST arm vs 13 BA arm, p=0.15) and 99 required TVR [44 (19%) ST arm vs 55 (24%) BA arm, p=0.25). TVR included PCI in 75 P (32 ST arm and 43 BA arm, p=0.2) and CABG in 27 (14 ST arm and 13 BA arm) (non-exclusive events). Any major adverse event occurred in 52 P in the ST arm (23%) and 65 (29%) in the BA arm (RR 0.81, 95%CI 0.58-1.10, p=0.19). On univariate analysis unstable angina (p=0.079), time to RE (p=0.013), diffuse (>10 mm) RE (p=0.08), baseline minimal lumen diameter (MLD)(p=0.05), TIMI flow 1-2 (p=0.029), %diameter stenosis (p=0.036), B2-C lesions (p=0.13), lesions at bifurcation (p=0.15), ostial location (p=0.14) and saphenous vein grafts (SVG)(p=0.005), were predictive of events at FU. In addition, when procedural data and results were examined: BA therapy (p=0.18), cross-over requirement (p=0.09), residual dissection (p=0.003), final pressure (p=0.04) and balloon/artery ratio (p=0.1) were also associated with events. On multivariate Cox regression analysis, time to RE (HR 1.96, 95%CI 1.4-2,9, p=0.001), baseline MLD (HR 0.64, 95%CI 0.4-1.06, p=0.07) and SVG (HR 5.8, 95%CI 2.3-14.5, p=0.003) were independent predictors of events.
Conclusions: P with in-ST RE undergoing repeat PCI have a relatively high event-rate at FU. Clinical, anatomic and procedural variables are predictive of the long-term clinical outcome in these P.

P2887 Mildly elevated serum creatinine levels are associated with impaired long-term outcome after coronary angioplasty

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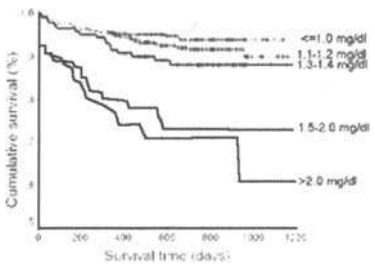
Patients with moderate renal failure and creatinine (crea) levels of 1.6-2.0 mg/dl were shown to have a significantly higher long-term mortality after PTCA. To evaluate a possible crea threshold for significantly reduced outcome, we performed a retrospective analysis of our PTCA patients from 1998-1999.
During these 2 years, 1,104 patients underwent a total of 1,440 PTCA procedures. Patients with endstage renal failure requiring maintenance hemodialysis (n=51) were excluded. Follow-up of the remaining 1053 patients was 99.6% complete. Patients were divided in 5 groups by their baseline crea: <=1.0 (n=437), 1.1-1.2 (n=376), 1.3-1.4 (n=132), 1.5-2.0 (n=55), and >2.0 mg/dl (n=39). Between these groups, significant differences were found concerning higher age and lower proportion of women with increasing crea levels, whereas risk factors as hypertension, dyslipidemia, smoking and diabetes differed non-significantly between the groups. During follow-up (mean 1184 days; 95% CI 1164-1204 days), 96 deaths and 46 non-fatal infarctions occurred. Univariate analyses identifid age (OR 1.03), multi-vessel disease (OR 1.21), ejection fraction (OR 0.96), previuos PTCAs (OR 0.42), previuos bypass grafting (OR 1.57), crea levels (OR 2.20), use of beta-blockers (OR 0.45) or of statins (OR 0.41) to be associated with death. Cumulative survival was displayed by a Kaplan-Meier model (fig.), with a significantly increased mortality at a crea of 1.3-1.4 mg/dl (p = 0.0108, log rang). Logistic regression analysis confirmed the above factors to be independent predictors of death, with an over-all accuracy of the model of 90.2%. Even mildly elevated crea levels of 1.3-1.4 mg/dl (indicating a 50% reduction in renal function) were associated with significantly higher long-term mortality after PTCA.



Survival after PTCA and creatinine.

P2888 Preprocedural C-reactive protein is associated with death/myocardial infarction but not with repeat revascularization following PTCA

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Background: We investigated the prognostic value of a preprocedural C-reactive protein concentration in patients undergoing percutaneous coronary angioplasty for the prediction of death, non-fatal myocardial infarction or repeat during 14 months follow-up. **Methods and Results:** Preprocedural plasma levels of C-reactive protein (CRP) were measured in 1458 consecutive patients undergoing coronary angioplasty. The incidence of death or myocardial infarction was 6.1%(44/716) in patients with a increased CRP level (>3 mg/L) and 1.5%(11/742) in patients with a normal CRP level (RR 4.35, 95% CI: 2.23 – 8.49). Survival without death or non-fatal MI was significantly lower in patients with an increased CRP versus patients with a normal CRP (log-rank 22.11, p<0.00001). Multivariate logistic regression analysis identified an increased CRP level as a strong independent predictor of event-free survival (RR 3.94; 95% CI 1.99 – 7.79, p=0.0001). Incidence of repeat revascularization was not different between patients with or without an increased preprocedural CRP (21% versus 19%, p=0.46). Statin therapy was associated with a lower mean preprocedural CRP (5.75 mg/L versus 7.17 mg/L, p=0.018) but was not associated with a lower incidence of death, non-fatal MI or repeat revascularization in this study. **Conclusion:** An increased preprocedural plasma C-reactive protein is a powerful independent prognostic indicator for the occurrence of death or non-fatal MI following coronary angioplasty, but it is not associated with the need for repeat revascularization.

P2889 Pre-procedural inflammation markers predict myocardial damage at the time of PCR in patients with stable angina

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The predictive value of inflammatory markers has been studied in various clinical contexts in patients (pts) with coronary artery disease. Little is known however, on the value of these markers in pts with stable angina treated by PTCA. We studied the predictive value of C reactive protein (CRP) and fibrinogen measured at baseline in 91 consecutive pts who underwent PTCA in year 2000. Pts with a recent (<1 month) myocardial infarction were excluded. Post-procedural rise in troponin I (>0.6 mg/L) and major in-hospital events (death, MI, stroke) were used as endpoints. For analysis, the population was grouped into tertiles according to pre-procedural levels of CRP (1st tertile<2 mg/l; 2nd tertile: 2-5 mg/l; and 3rd tertile>=5 mg/L) and fibrinogen (1st tertile<3.3 g/L; 2nd tertile:3.3-4 g/L; and 3rd tertile>=4 g/L). Tertiles of CRP or fibrinogen were predictors of post-procedural rise in troponin (myocardial damage) (p=0.003 and p=0.02, respectively). The same trend was found for in-hospital cardiac events (p=0.09 and p=0.07, respectively). Importantly, tertiles of CRP and fibrinogen remained predictors of myocardial damage and in-hospital events after exclusion of pts with unstable angina at baseline (see table).

Events according to markers at baseline

	All patients (n=91)		Patients with stable angina (n=63)	
CRP	Troponin rise	Clinical events	Troponin rise	Clinical events
1st Tertile	(0/29) 0%	(0/29) 0%	(0/26) 0%	(0/26) 0%
2nd Tertile	(6/29) 20.7%	(1/29) 3.4%	(2/15) 13.3%	(0/15) 0%
3rd Tertile	(11/33) 33.3%	(4/33) 12.2%	(6/22) 27.3	(2/22) 9.1%
p	0.003	0.09	0.018	0.13
Fibrinogen	Troponin rise	Clinical events	Troponin rise	Clinical events
1st Tertile	(1/30) 3.3%	(0/30) 0%	(1/25) 4.0%	(0/25) 0%
2nd Tertile	(8/29) 27.6%	(1/29) 3.4%	(2/19) 10.5%	(0/19) 0%
3rd Tertile	(8/31)25.8%	(4/31) 12.9%	(5/18) 27.7%	(2/18) 11.1%
p	0.02	0.07	0.06	0.07

Conclusion: In pts with stable angina, baseline levels of CRP and fibrinogen are predictors of myocardial damage and in-hospital events. Our results suggest that in pts usually considered to be at low risk for angioplasty, preprocedural measurement of CRP and/or fibrinogen may help to select a "high risk" group.

P2890 Insulin sensitivity and nitric oxide release during oral glucose tolerance test are strong predictors of restenosis after coronary stenting

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Background: Hyperinsulinemia and diabetes mellitus lead to accelerated atherosclerosis and increased restenosis after percutaneous transluminal coronary angioplasty (PTCA) and stent implantation. However, the correlation of the metabolic alterations typical of the Insulin Resistance Syndrome with restenosis after stenting has not been established and was studied in this prospective single center observational trial.
Materials and Methods: An oral glucose tolerance test (OGTT) was performed in all 69 patients (mean age=57±2 yrs, mean body mass index 26.2±0.4 kg/m^2) with normal baseline glucose levels who underwent routine angiographic control 6 months after coronary stent implantation.
Results: Angiographic restenosis (> 50% DS) after stenting was found in 28 pts (group 1), with a Minimal Lumen Diameter (MLD) of 0.93 ± 0.10 mm (3.0±0.31 mm; in the 41 pts without restenosis, group 2, $p<0.0001$). There were no significant differences in MLD between the two groups before-and after intervention.
Group 1 showed higher HOMA (homeostasis model assessment) (2.4±0.2 vs 1.9±0.1, mmol/l x μU/ml $p<0.03$), C-peptide levels (2.4±0.1 vs 2.0±0.1 ng/ml, $p<0.01$) and homocysteine levels (13.3±0.8 vs 11.3±0.6 μmol/l $p<0.03$). Insulin response after OGTT was also significantly increased in group 1: insulin incremental areas were 7733±773 μU/mL in group 1 vs 5595±400 μU/mL in group 2 [(0-120 min); $p<0.01$] while no differences were found measuring incremental areas (0-120 min) of glucose levels after OGTT in both groups. Using a mathematical deconvoluted method, in group 1 insulin sensitivity was decreased (5.0±0.6 vs 7.4±0.8 10^{-4} mmol kg^{-1} min^{-1}/μU ml^{-1}; $p<0.05$) and insulin secretion was increased (1.0±0.1 vs 0.8±0.01/μU ml^{-1}/mg dl^{-1}; $p<0.05$). Group 1 showed also a significant decrease of nitric oxide (NOx) incremental area during OGTT [-480±157 vs 143±117 μmol/l (0-120 min); $p<0.002$. At simple regression analysis, MDL at follow-up was positively correlated with insulin sensitivity during OGTT ($r=0.52$; $p<0.001$), C-peptide ($r=0.26$; $p<0.05$), proinsulin ($r=0.31$; $p<0.03$), HOMA ($r=0.25$; $p<0.05$) and NOx incremental area ($r=0.39$; $p<0.002$). At multiple regression analysis only insulin sensitivity during OGTT ($p<0.001$) and NOx incremental area ($p<0.03$) were independently correlated with MLD.
Conclusions: Insulin sensitivity and NOx release during OGTT predict restenosis after stenting in patients with CAD.

P2891 Increased CD15 on leukocytes and decreased platelet activation in the coronary sinus after coronary intervention: implications for restenosis

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The identification of marker associated with coronary stenosis is necessary for the development of therapeutic strategies that improve the clinical outcome of patients undergoing coronary intervention. The study examined alterations in platelet- and leukocyte-associated adhesion proteins during angioplasty in patients with stable coronary artery disease. The aim was to identify whether the presence of activation-dependent adhesion proteins on platelets and CD15 on leukocytes in the coronary microcirculation was associated with the occurrence of restenosis.
Circulating platelets and leukocytes were obtained from the coronary sinus before and directly after successful coronary intervention (balloon angioplasty (n=8) or stent implantation (n=15). Adhesion protein density on leukocytes (CD 15 and L-selectin) and on platelets (P-selection, thrombospondin and CD41) was flow cytometrically measured. Levels of adhesion proteins pre and post intervention were related to the occurrence of restenosis as assessed by re-angiography after 6-8 months.
CD15 on leukocytes was the adhesion protein marker that was significantly higher pre and post intervention in patients who developed restenosis (n=8) compared to those without restenosis (n=15) (CD15 immunofluoresence for patients with restenosis 187±87 versus 118±55 for patients without restenosis, $p<0.01$). CD 15 on leukocytes and activation-dependent adhesion proteins on platelets were significantly reduced post compared to pre coronary intervention in all patients (for p-selectin-positive platelets 8.1% [9.5;5.1] pre vs 5.2% [6.5;4.6] post PCI; for thrombospondin 31% [37;22] pre vs. 17% [27;9] post PCI). The reduction in adhesion proteins on cells was accompanied by a reduction in the platelet count.
Increased CD15 expression on leukocytes pre and post intervention is associated with the occurrence of restenosis. Leukocyte CD15 expression and platelet consumption contribute to the development of coronary restenosis post intervention. Inhibition of leukocyte adhesion via CD15 antagonism may prove to be useful for preventing restenosis.

P2892 The changes and the prognostic impacts of the levels of secretory type II phospholipase A2 and CRP in CAD patients after coronary intervention

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Background: A2 phospholipases are a family of enzymes that can hydrolyze phospholipids at the sn-2 position to generate lysophospholipids, fatty acids, and precursors of various pro-inflammatory lipid mediators. This enzyme might be involved in modifying plaque remodeling after rupture in the artery wall. The circulating levels of secretory type II phospholipase A2 (sPLA2) are found to be increased in patients with CAD. The increased levels of several inflammatory markers as C-reactive protein (CRP) and sPLA2 were known to be strong risk factors for prognosis. These inflammatory markers may play a role in the pathogenesis of acute coronary syndrome with the rupture of an atherosclerotic arterial plaque. The present study was designed to evaluate the changes of the level of sPLA2, inflammatory and cardiac injury markers before and after mechanical plaque rupture created by percutaneous coronary intervention (PCI) in CAD patients and their prognostic impact at future coronary artery events.
Methods and Results: Plasma levels of sPLA2, CRP and other cardiac enzymes were measured in 120 consecutive patients with CAD by ELISA. Five serum samples as: (1) before and (2) after diagnostic angiography, (3) after PCI, (4) 24-hours after PCI and (5) 48-hours after PCI respectively. The sPLA2, CRP didn't change after the procedures of diagnostic angiography ($p=0.7$, 0.1 respectively). However, the level of sPLA2 significantly (average 2-fold, maximally 10-fold, $p<0.0001$) increased after PCI. The level of CRP and the other cardiac enzymes didn't rise up immediately after PCI ($p=0.5$) but elevated significantly later at 24 hours after intervention ($p=0.02$). The levels of sPLA2 and CRP were persistently higher after 48-hour duration but the cardiac enzymes declined rapidly after 24 hour. After a 2-year follow up period, the level of sPLA2 after PCI, severity of CAD, smoking and hypertension remained independent risk factors for furture acute coronary event (OR=2.3, 2.1, 3.4 and 4.1 respectively).
Conclusion: Data from the present study had shown that the procedure of PCI might result in immediate elevation of circulating level of sPLA2 following the mechanical disruption of coronary plaque and the elevated levle of sPLA2 had significant prognosis. The CRP level and the traditional cardiac enzyme such as CK, CK-MB and troponin T didn't rise immediately but increased at 24 hours after PCI. These results strongly suggest that sPLA2 not only played as a pro-inflammatory factor and also might contribute in the pathogenesis of atherosicerosis and acute coronary syndrome.

P2893 Clinical long-term results of coronary angioplasty (PTCA) in degenerated bypass grafts (CABG)

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The frequency of coronary artery bypass grafting is still increasing. Prior to 1990, the majority of these patients received venous grafts. However, a moderate cohort suffered from angina petoris or myocardial infarction over time due to either progression of atherosclerosis or degeneration of the CABG.
Between 1988 and 2000 more than 8,000 PTCA procedures were performed at our institution. From these procedures were performed in 424 bypass grafts (5.3%) on 294 patients. This patient group (257M; 37F) had a mean age of 65 (± 10,3) years and the time between CABG and PTCA was 7,1 (±4,8) years.Using a local data base all patients were evaluated for interventional technique, individual risk factors, CCS-classification and angiographic data. Clinical long-term follow up was taken by questionnaire and telephone contact with practitioners and patients.
218 patients (74%) underwent PTCA once, 76 had more than one PTCA. The initial success rate was 94%. A total of 165 (60%) of these underwent control angiography 3 - 6 month later. Restenosis rate (50% diameter stenosis) was found in only 20%.
Clinical follow-up by questionnaire was performed 4,6 (±3,1) years after PTCA and 79% of patients answered the questionnaire. 190 patients with a successful PTCA in CABG were still alive and in CCS-class I - II. Of these, 80% were content with their physical condition. In those patients who died in-between the cause of death was non-cardiac in 56% and cardiac in 44%.
In conclusion, PTCA in degenerated CABG can be performed with a high initial success rate, followed by a moderate restenosis rate of 20%. The late clinical outcome in this high risk group is very satisfying.

PAEDIATRIC ARRHYTHMIA/ELECTROPHYSIOLOGY

P2894 Arrhythmia in children with complex congenital heart defects and functionally single ventricle after Fontan procedure

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The ultimate stage of surgical treatment employed in patients (pts) with complex congenital heart defect (CCHD) and functionally SV is a modified Fontan (F) procedure. Arrhythmia (arh) and conduction disturbances are important risk factors influencing SV function, decreasing its efficiency and being among reasons for long term prognosis deterioration.

The aim of the study was a retrospective assessment of the incidence of various types of arh in children with CCHD and SV after Fontan operation in the early and late postoperative period.

Material/methods: Ninety-seven pts with CCHD and SV who underwent F procedures in the years 1982-2000 were examined. Twenty-three of them underwent direct F, while 74 - staged F procedure. ECG tracings after F palliation were analyzed in the following time slots: A) once a week up to 1 mo, B) every 3 mo, up to 1 yr, C) every 6 mo, for 2-5 years, D) every 6 mo, over 5 years. Correlation between incidence of arh and type of the ventricular loop (D or L) were also analyzed.

Results: The results are shown in the table. The percentage of cases with diagnosed arh in patients currently followed up increased in time and in the defined slots: A) 16.5% (16/97), B 27% (26/97), C) 31% (24/77), D) 50% (13/26). Among 36 pts with arh, various forms of sinus node dysfunction were observed in 33 cases while atrial flutter (AF) was diagnosed in 3 pts. Complete atrioventricular block was not observed. In children with ventricular D-loop arrangement or HLHS, the incidence of arh was similar (33%) and it was lower than in pts with CCHD and SV with ventricular L-loop. Three pts with AF needed pharmacological therapy while 2 other pts - pacemaker implantation.

Ventricles	NO	Without arh	New arh				Total arh
			1 mo post op	1 yr post op	2-5 yrs post op	>5 yrs post op	
D-loop	60	40	11	4	2	3	20
L-loop	28	15	5	4	3	1	13
HLHS	9	6	0	2	1	0	3
Total	97	61	16	10	6	4	36

arh- arrhythmia, op - operation

Conclusions: The risk of arh in children with CCHD and functionally SV after F procedure is the highest in the early postoperative period and generally is higher among pts with concomitant L-loop ventricular arrangement. The number of pts with arh increases gradually in the time of observation.

P2895 Predictive value for malignant arrhythmias of echo and signal averaged electrocardiogram indices in repaired tetralogy of Fallot: long-term follow-up

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We have reported that abnormal signal averaged ECG (SAECG), (RMS<=23mV, LAS>=32.5ms, fltQRS>=148msecs) and echocardiographic (ECHO) variables, (right ventricular diameter/left ventricular diameter: RVD/LVD>=1.05) are associated with potentially malignant ventricular arrhythmias on Holter recordings of asymptomatic patients (pts) with repaired Tetralogy of Fallot. In this study we aimed at detecting the predictive value of the aforementioned indices for the occurrence of sustained VT, after a 5 year follow-up period.

Methods: Forty pts 32±10 years old with repaired Tetralogy of Fallot were followed in our department for a period of 60 months. Pts were divided into two groups; Group A: 8 pts who had abnormal SAECG along with abnormal ECHO indices at baseline and Group B: 32 pts with no abnormal parameters of the SAECG and/or of the ECHO.

Results: Three of group A pts developed sustained VT after a follow-up period of 32, 36 and 40 months, respectively. Positive predictive value was 37%. No one of the group B pts developed abnormal SAECG along with ECHO indices. Also no one developed malignant arrythmias; negative predictive value 100%. The cumulative Kaplan Mayer event-free survival curve differentiated significantly between the two groups (p=0.038).

Conclusions: Our present data indicate that pts with repaired Tetralogy of Fallot and abnormal SAECG and ECHO indices have a 37% PPV to develop malignant arrhythmias. However, pts without abnormal indices have a high NPV for event free follow-up period of 60 months.

P2896 Volume-related mechano-electrical feedback in humans: assessment through monophasic action potential

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Background: Basic research and animal experiments have shown the development of electrophysiological changes during or after changes in mechanical loading. The aim of the present study was to assess the presence of volume-related mechano-electrical feedback in humans, evaluating dispersion of ventricular repolarization time indexes and monophasic action potentials (MAP) following acute changes in ventricular volume overload in humans.

Methods: The study group comprised 16 consecutive pts (4M/12F, aged 4-36years) affected by ostium secundum atrial septal defect (ASD) with moderate to severe right chambers volume overload signs, who underwent successful ASD device closure. Dispersion of ventricular repolarization time was evaluated before and after the ASD closure through measurement of QT and QTc dispersion (QTD, QTcD), JT e JTc dispersion (JTD,JTcD) and T-peak to T-end interval (Tp-Te). MAP were recorded by contact electrode catheter introduced via femoral vein and advanced into the RV apex. MAP duration (MAPd), determined at a repolarization level of 90% with respect to the MAP amplitude, was measured on the electrophysiological traces recorded before and after volume-overload release.

Results: After ASD closure patients showed a significant decrease in QTD (48.9±24.8 vs 29.7±13.5; p<0.0002), in QTcD(62.5±21.5 vs 45.5±15.6; p<0.0001), in JTD (54.7±22.2 vs 41±14.2; p<0.02), in JTcD (60.4±19.6 vs 47.5±16.9; p<0.02), in Tp-Te (112.3±12.2 vs 106.8±12.6; p<0.02). Furthermore patients showed a significant increase in MAPd (355±24.4 vs 366.8±24.9; p<0.0001)

Conclusion: Changes in haemodynamic loading can produce electrophysiological effects in humans. Acute reduction in ventricular volume overload, following ASD device closure decreases electrical instability, as expressed by dispersion of ventricular repolarization time shortening and monophasic action potential duration increasing.

P2897 Is routine echocardiography valuable after uncomplicated catheter ablation in children?

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Introduction: Although the complication rate of radiofrequency catheter ablation (RFCA) procedures in children is low, clinically asymptomatic complications do occur. Transthoracic echocardiographic studies are performed after every RFCA in children in most centers. We determined the clinical value of routine echocardiography performed after catheter ablation of supraventricular tachycardia (SVT) in children.

Methods and Results: Between April 1996 and September 2001, 138 children (75M, 63F), (mean age 13 years; range 0-19 years), underwent 160 uncomplicated radiofrequency catheter ablation (RFCA) procedures for SVT at our two institutions. In every child a transthoracic 2-D echocardiogram (TTE) with Doppler was performed before and after the procedure.

The mechanisms for SVT were Wolff-Parkinson-White syndrome in 48, concealed accessory pathways in 41, AVNRT in 42, PJRT in 2, junctional ectopic tachycardia in 1, sinus node reentry tachcardia in 1 and focal atrial tachycardia in 3 patients. The pre-ablation TTE's in all cases were normal.

After RFCA, in 4 clinically asymptomatic patients the TTE revealed procedure-related complications: one patient (age 15 years) with focal atrial tachycardia, showed mild aortic valve insufficiency. This had resolved spontaneously 6 months later; three other children developed an asymptomatic pericardial effusion. In 2 patients (a 11 year old with a concealed left sided accessory bypass and a 16 year old with AVNRT) this resolved spontaneously, but the third patient (aged 9 years, with a concealed left lateral pathway) required pericardiocentesis. The same 9 year old patient also developed a clinically asymptomatic mild aortic insufficiency, which resolved spontaneously within 6 months.

Conclusion: Echocardiography after uncomplicated RFCA procedures in children may detect asymptomatic complications. This is particularly relevant in the current management involving same-day discharge after uncomplicated catheter ablation in children.

P2898 Long-term follow-up after ablation of atrial tachycardias in patients with congenital heart disease using three-dimensional mapping techniques

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Introduction Atrial tachycardias in pts with surgically corrected congenital heart disease (CHD) are often reentrant tachycardias (ART) with complex conduction pathways through scar tissue. 3-Dimensional mapping techniques for selection of target sites and accurate delineation of areas of scar tissue are therefore mandatory. This study evaluated the long-term outcome after ablation guided by 3-D electro-anatomical mapping techniques for identification of the arrhythmogenic substrate in pts with CHD and ART.
Methods Pts (n=52, age 38±14 yr., 22 male) with ART and tricuspid atresia (20), transposition of the great arteries (13), atrial septal defect (13), Fallot (6) referred for catheter ablation of atrial tachycardias were studied using the CARTO or Loca Lisa system. Detailed activation/voltage maps were constructed to localize anatomically and surgically created barriers during ART and to mark sites ablated. Scar tissue was delineated using a cut-off value of 0.1 mV.
Results Mapping was performed during ART (CL 294±79 ms, no. of induced ART per pt: 1.3±0.7). Termination of ART was achieved by creating a line of conduction block 1) between areas of scar tissue (24%) 2) at the cavo-tricuspid isthmus (51%) or 3) both (24%). In 2 pts, IART converted to atrial fibrillation (AF) during RF. Success (non-inducibility after RFCA) was achieved after 1 or 2 (n=4) procedures in 76% of the pts. No complications were observed. During follow-up (14±6 months), 76% of the pts had sinus rhythm, 19% paroxysmal and 5% permanent AF.
Conclusion Pts with ART and CHD can be successfully treated by 3-D electro-anatomical mapping guided ablation. This technique facilitates detailed identification of the arrhythmogenic substrate and selection of target sites for ablation.

P2899 Pacemaker-implantation before 30 years of age – Prevalence, indications, complications and long-term follow-up

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In our database of 6465 patients (pts) with pacemaker (PM), 80 pts (1.2%) underwent first implantation before 30 years of age (median age 16.3 years). The morbidity and mortality of these young pts are widely unknown.
The median follow-up was 57.9 months (0.03-346 months); follow-up was performed after 6 or 12-month intervals in all 80 pts (33 women). Indications for implantation were: AV-block in 58% (46 pts), sick sinus syndrome in 33% (26 pts) and other bradyarrhythmias in 6% (5 pts). The causes for arrhythmia were: previous heart surgery (32 pts, 40%) or congenital bradyarrhythmia (8 pts, 10%); etiology was unknown in 50%.
At first implantation a transvenous approach was used in 79%. 41 pts (51%) received a single-chamber system (later dual-chamber system in 22% of these pts); 26 pts (33%) received a dual-chamber system at first implantation.
In long-term follow up 0-8 re-operations were required (mean 0.95; median longevity of PM systems 46.9 months). Indications for re-operation were: battery depletion (55.3%), infection/wound healing problems (10.5%), fracture or dislocation of pacing leads (11.8%) and malfunction of the electric system (5.2%). During follow-up, PM was no longer necessary in 7 pts (8.8%). 16 pts died (20%; 56.3% after heart surgery, 6.3% with congenital arrhythmia, 6.3% with cardiomyopathy, 31.3% with unknown etiology). Pts died 28.5 months after first implantation (1-164 months); sudden death occurred in 9 pts.
Congenital and corrected heart malformations are the main indications for PM implantation before 30 years of age. The mortality rate and the rate of sudden deaths are surprisingly high.

UPDATE ON SURGICAL TECHNIQUES

P2900 Off-pump coronary artery bypass surgery does not reduce lymphocyte activation

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Background: Coronary artery bypass surgery is known to be associated with alteration of inflammatory mediators and immune function, with early phase lymphocyte activation, that could be responsible for post-operative lymphopenia and lymphocyte unresponsiveness. In this trial, we test the hypothesis that off- pump coronary bypass surgery might result in less lymphocyte activation than on-pump coronary surgery.
Methods: We studied lymphocyte activation response during the operative and post-operative period in 28 patients randomized to off-pump coronary surgery (n = 13) or conventional on-pump coronary surgery (n = 15) using flow cytometry to determine expression of CD23, CD25, CD26, CD69 and DR on T (CD3+) and B (CD19+) lymphocytes in the peripheral blood.
Results: There were no significant differences in any of the lymphocyte activation markers off-pump compared to on-pump coronary surgery (2 way ANOVA for repeated measures, $P > 0.05$). Considering all patients studied, there was an elevation of the proportional expression of CD69 and CD25 in T (CD3+) and B (CD19+) lymphocytes. In T lymphocytes, the higher proportional median value (± SE) of CD69 was observed 6 hours after completion of anastomosis (+75 ± 476%), and CD25 had a more gradual elevation, with its peak median value (+48 ± 24%) occurring 24 hours after revascularization. In B-lymphocytes, CD69 peak median value (+104 ± 269%) occurred also 6 hours after the end of anastomosis. CD25 had its peak median value (+150 ± 773%) 12 hours after revascularization and its last measured value was elevated. The expression of CD 26 in T lymphocytes had an apparent decrease in proportional median values (-42 ± 32%) 12 hours after end of anastomosis.
Conclusions: 1) Compared to on-pump cardiopulmonary bypass, off-pump surgery does not reduce lymphocyte activation. 2) Coronary bypass surgery results in early activation of lymphocytes, with increased expression of CD69 and CD25 on T (CD3+) and B (CD19+) peripheral blood cells. The early elevation of CD69, and late elevation of CD25, may indicate two parts of a sequence of lymphocyte activation. (Supported by FAPERGS)

P2901 Complete arterial coronary revascularization avoiding median sternotomy for diabetics

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Introduction: The use of both internal mammary arteries (BIMA) in coronary artery bypass grafting (CABG) is proposed for better graft patency, but is related to increased sternal wound complications. Up to now minimally invasive techniques avoiding sternotomy with BIMA grafting were hardly feasible. The introduction of a wrist-enhanced robotic system enables harvesting of BIMA without sternotomy via three one cm stab wounds. A small left lateral chest incision allows complete arterial revascularization using regular cardiopulmonary bypass.
Methods: Fifty patients (37 male, 13 female, aged 65 ± 8.5 years, LVEF 67 ± 10.7%) were treated for coronary artery disease. 72% were diabetics. Both IMAs were harvested via three ports using the da Vinci™ surgical robotic system. Access to the heart for central aortic cannulation for institution of cardiopulmonary bypass and for coronary anastomoses was achieved via a 6 to 8 cm left lateral chest incision at the level of the 2nd intercostal space.
Results: In the series one patient died due to pneumonia on postoperative day 16. Conversion rate to median sternotomy was 4%. Duration of surgery was 237.5 ± 74.5 min, ICU stay was 22 ± 19.1 hrs, ventilation time 4.3 ± 10.9 hrs, and total hospital stay 7 ± 1 days, respectively. Grafts per patient was 2.1.
Conclusion: Total arterial revascularization using BIMA grafting was applied in 72.9%. There were neither sternal instabilities nor deep wound infections.
This minimally invasive approach allows total endoscopic BIMA harvesting using three one cm ports only. Via a small left lateral chest incision the use of BIMA for CABG is possible. Risk of developing sternal wound complications in diabetics is decreased.

P2902 Coronary bypass grafting combined with mitral valve anuloplasty in severe ischaemic dilated cardiomyopathy

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Mitral valve surgery combined with bypass grafting in patients with severe dilated ischemic cardiomyopathy (SDIC) is a timely matter. Mitral valve replacement combined with coronary bypass is still associated with high hospital or surgical mortality. Coronary bypass alone seems to be useful when mitral regurgitation is moderate; mitral valve anuloplasty in association with surgical coronary revascularization appears to be promising safe procedure for containing severe mitral insufficiency.

Thus, we have evaluated at six months the influence of surgical myocardial revascularization plus mitral valve anuloplasty on clinical and echocardiographic parameters of left ventricular function in patients with SDIC and severe mitral incompetence. Fifteen patients (group A) aged 68±4 years, with SDIC (at angiography left ventricular ejection fraction (LVEF) = 26.4±5.3%) and severe mitral regurgitation (ERO > 0.2 cm^2) were submitted to coronary bypass and mitral valve repair with Cosgrove ring; 13 patients (group B) aged 64±8 years with SDIC (at angiography LVEF = 27:8±5.3) and mild or moderate mitral incompetence served as control group. Before and six months after operation both groups underwent an echo-Doppler evaluation of left ventricular function parameters.

Operating risk (Euroscore), extracorporeal circulation time and aortic clamping time were significantly higher in group A than in group B (6.5±1.5 vs 3.3±1.6 $p < 0.001$, 144±43 vs 103±50 min $p < 0.005$ and 96±20 vs 53±23 min $p < 0.001$ respectively).

Hospital and perioperative mortality were absent, whereas at 6 months they were 6% in both groups; LVEF increased in both group A (from 31±6 to 42±7% $p < 0.001$) and group B (from 32±7 to 44±7 $p < 0.001$); end-systolic volume and wall motion score index significantly and similarly decreased in both groups (group A: from 139±60 to 121±67 ml $p < 0.05$ and from 1.9±0.4 to 1.5±0.4 $p < 0.01$; group B: from 122±48 to 96±35 ml $p < 0.05$ and from 2.2±0.3 to 1.5±0.4 $p < 0.01$, respectively). Both groups showed a significant and similar increase in peak E velocity and peak E/A velocity ratio.

It is noteworthy that patients with SDIC, who are at very high surgical risk, showed low mortality at 6 months; in addition in these patients mitral valve anuloplasty did not produce a further increase in hospital, surgical or late mortality. Finally a significant improvement of left ventricular systolic and diastolic function was observed in all patients treated with coronary bypass alone or in combination with mitral valve anuloplasty.

P2903 Up to six years performance of in vitro seeded vascular endothelial cells onto small diameter vascular grafts in coronary bypass surgery

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Objective: Each year more than 300.000 coronary bypass operatioms are performed worldwide. As the number of patients with re-operations and insufficient bypass material is increasing, several alternatives to autologous material are under investigation. This feasibility study was performed to investigate the combination of small-diameter polytetrafluorethylene (PTFE) grafts seeded with viable autologous vascular endothelial cells (AVEC) to use in coronary bypass surgery.

Methods: Between September 1995 and December 1998 fourteen patients (median age 71 years, range 61-79 years) received 21 AVEC seeded small-diameter PTFE grafts. Forty-three percent of the performed implantations were reoperations, including one aortic valve replacement. The AVEC were harvested from a patient's forearm vein. At the cell culture laboratory, the endothelial cells were isolated, expanded and characterized until a sufficient number of cells were available. The in vitro seeded grafts were conditioned for 7 days prior to the implantation.

Results: Cumalative total data collected represents 58 patients years and was 100% completed. The seeded AVEC density was 105.000 cells/cm^2 with a cell viability of 95.5%. The patency rate at up to 73 months was 81% confirmed by angiography. Angioscopy and intravascular ultrsonography showed no atheromas or stenosis in 17 out of 21 grafts. Two asymptomatic occlusions were verified at 20 and 66 months post-operatively and two symptomatic occlusions were seen immediately after operation and at 34 months postoperative.

Conclusions: AVEC seeding seems to increase the patency rate of small caliber PTFE grafts.

P2904 Clinical evaluation of a new decellularized pulmonary homograft

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Objective: Homograft valve implantation induces a potentially detrimental immunological response. Theoretically, any such response may be aborted by tissue-engineering. A novel cryopreserved decellularized homograft valve [Synergraft™] offers the unique opportunity to gain new insight into the immunology of homograft implantation and its significance for valve function.

Methods: 14 patients (10 male, 4 female; 41.5 ± 10.9 years) were operated upon. Implantation of the pulmary Synergraft (mean diameter 25.3 ± 1.3 mm) was performed as part of a Ross-procedure in 11 patients. Postoperatively, echocardiography and anti-human-leucocyte-antigen [HLA] class I antibody determination were performed 1, 3, and 6 months postoperatively. The results were compared to those in our Ross-operation database.

Results: During follow-up, no patient became positive for anti-HLA antibodies. In contrast, 73% of patients receiving conventional cryopreserved pulmonary homografts are positive for anti-HLA antibodies 6 months postoperatively.

The Synergraft showed good hemodynamic performance: the pressure gradients were low and increased only slightly and non-significantly during follow-up (Dpmean: 3.6 ± 1.6 to 5.2 ± 2.5 mmHg; p=.26). Correspondingly, the effective valve orifice area [EOA] indexed for body-surface area showed only a small, non-significant decrease (1.46 ± 0.30 to 1.30 ± 0.26 cm^2/m^2; p=.30).

Patients receiving a conventional cryopreserved homograft usually show a moderate, increase of the pressure gradients during the first 6 months postoperatively (2.8 ± 1.8 to 5.9 ± 3.1 mmHg; p=.05) corresponding to significant decreases of the EOA.

Conclusions: Implantation of a decellularized, cryopreserved pulmonary homograft appears to be associated with significantly less immunization of the recipient. The short-term hemodynamic performance of the Synergraft is promising. Due to the small patient number and the short follow-up period, it cannot be determined whether the hemodynamic performance of the Synergraft differs from that of conventional cryopreserved homografts.

P2905 Early clinical results of RVOT reconstruction with a tissue engineered pulmonary valve; report of seven consecutive patients

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Objective: Biological and mechanical prostheses for aortic valve replacement have important limitations due to limited durability or thromboembolism and hemorrhage. Viable pulmonary autografts showed that these disadvantages could be overcome. However, the right ventricular outflow (RVOT) tract has to be reconstructed. The aim of the study was to demonstrate for this purpose the safety and feasibility of viable tissue engineered heart valves, seeded with autologous vascular endothelial cells.

Methods: Since April 20, 2000 seven consecutive patients underwent pulmonary valve replacement with a tissue engineered pulmonary valve. A piece of vein was harvested and endothelial cells were isolated, expanded and characterized. After sufficient numbers of viable vascular endothelial cells were available pulmonary allografts were decellularized and seeded with endothelial cells in a bioreactor. Sterility of the heart valves were proved before implantation into the RVOT. Follow-up was performed by clinical evaluation, transthoracic echocardiography (TTE), magnetic resonance imaging (MRI) and multi-slice computed tomography (MS-CT).

Results: Patients age ranged from 28 - 55 years, median 46 years. All patients were male and survived the operation. Preoperative NYHA classification improved in all patients. TTE evaluation of the neo-aortic and tissue engineered heart valve are summarized in the table. MRI showed improvement of the LV-function without RV-functional changes. The leaflets of this tissue engineered valve looked smooth and pliable without functional valve regurgitation. MS-CT showed no calcification up to 1.8 years of follow-up.

	discharge (n=7)	3 months (n=7)	6 months (n=6)	1 year (n=6)
TE heart valve				
MPG (mm Hg)	1.94 ± 0.69	1.66 ± 0.59	1.52 ± 0.41	2.00 ± 0.57
flow velocity (m/s)	0.77 ± 0.16	0.71 ± 0.16	0.59 ± 0.04	0.71 ± 0.08
regurgitation (trivial)	none	one	one	one

MPG = mean pressure gradient

Conclusions: Tissue engineered heart valves seeded with autologous cells showed excellent performance during short term follow-up. As these viable heart valves showed no structural degeneration and are living structures, they might have potential for growth, repair and remodeling. Thus, they may obviate the need for reoperation.

P2906 Early mitral ring annulolasty does not alter postinfarction ventricular remodelling in chronic ischaemic mitral regurgitation

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Introduction: The contribution of progressive ischemic mitral regurgitation to post-infarction left ventricular remodeling and heart failure is not well established.
Methods: Prior to producing a posterolateral infarction known to cause chronic mitral regurgitation in sheep, we performed mitral ring annuloplasty (Carpentier-Edwards PhysioTM) in one group (n=6) and compared them to a control group (n=6) with no annuloplasty. Both underwent an infarction of 24% of the LV mass localized to the posterolateral wall including the entire posterior papillary muscle. In both groups, transdiaphragmatic echocardiograms were obtained pre-infarction, 30 minutes post-infarction, and at 2, 5, and 8 weeks post-infarction to assess for MR and LV geometry and function. MR was graded on a scale of 1+ to 4+.
Results: Echocardiography confirmed that all infarcts were of similar size and location. Control group animals developed significant MR by 8 weeks. Annuloplasty group animals did not develop significant MR. The control and annuloplasty groups both experienced massive LV dilation at 8 weeks as demonstrated by large increases in end-systolic volume (ESV) and end-diastolic volume (EDV). LV ejection fraction (EF) decreased in both groups. LV end-diastolic pressure (LVEDP) rose similarly in both groups.

	Time	R (grade)	ESV (cc)	EDV (cc)	EF (%)	LVEDP (mmHg)
Control	Preinfarct	0.6 (±0.6)	37(±11)	61(±12)	38(±7)	0.9(±1.2)
	8 weeks postinfarct	3.4 (±0.5)	76 (±12)	112 (±15)	32 (±6)	5.1 (±0.9)
Ring	Preinfarct	0.6 (±0.5)	38 (±4)	69 (±12)	38 (±7)	0.4 (±0.6)
	weeks postinfarct	0.6 (±0.5)	78 (±4)	113 (±15)	25 (±4)	5 (±1)

Conclusions: In an ovine model of chronic ischemic mitral regurgitation, ventricular dilatation and dysfunction is not altered by early mitral ring annuloplasty.

P2907 Long-term follow-up 12 months after implantation of a biodegradable iron-zinc hybrid coil into the subclavian artery of New Zealand White Rabbits

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Objective: We conducted this study to evaluate the safety of the prototype of a biodegradable iron/zinc hybrid coil in a rabbit model. The primary objective of the study was to assess local and systemic toxicity. Secondary study objective was to analyze the primary and secondary occlusion rate of the novel coil.
Methods: 30 New Zealand White rabbits with a mean weight of 4,2 kg were sedated using midazolam and propofol. After intubation, anaesthesia was maintained with isofluorane. A femoral arterial cutdown was performed and the anatomy of the left and right subclavian artery was documented with selective angiographies. The implantation site was chosen distally to collateral vessels to prevent ischemia of the upper extremity. In 15 rabbits conventional MWCE coils (Cook, Bjaeverskov, Denmark) were implanted, 15 rabbits were received one to four hybrid iron/zinc coils. Residual patency of the vessel was documented by selective angiography. The femoral artery was ligated and the skin closed. Blood samples were drawn before and 3,6 and 12 months after the implantation. The rabbits were followed for 3 (n=9), 6 (n=9) and 12 months (n=9). Results: The primary occlusion rate was 100% for the MWCE coils, and 47% for the Fe/Zn hybrid coils. 1 rabbit in the MWCE group died due to pneumonia, 1 rabbit in the hybrid coil group died early postoperatively due to peritonitis, another rabbit of the hybrid coil group was sacrificed prematurely due to progressive palsy of the upper extremity. There was patency of the coil-laden subclavian artery at follow-up angiography in 1/ 14 rabbits of the MWCE coils and in 5/13 rabbits of the hybrid coil group. The mean serum levels for Fe were 31,39 μmol (Zn 49,18 μmol/l) prior to implantation and 31,35 μmol/l (Zn 46,20 μmol/l) at the last follow-up in the hybrid coil group. In the MWCE group the mean serum levels for Fe were 31,12 μmol (Zn 46,17 μmol/l) prior to implantation and 25,94 μmol/l (Zn 38,03 μmol/l) at the last follow-up. No local toxicity was encountered on histopathologic cutting-grinding specimens of the coiled subclavian artery. No excessive inflammatory response to the coil was observed. Examination of the heart, lung, liver, spleen, ovaries and kidneys showed no macroscopic or histopathologic signs of systemic toxicity neither in the hybrid coil nor in the MWCE group. Conclusion: Degradable Fe/Zn hybrid coils show no local or systemic toxicity 3 to 12 months after implantation into the subclavian artery of New Zealand White rabbits. Implantation of Fe/ Zn coils does not result in elevated serum iron or zinc levels.

P2908 Cryopreservation reduces antigenicity in allografts

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Background: There is a need for arterial grafts in coronary surgery, but donor fresh arterial grafts are useless because rejection. Cryopreservation is useful for banking purposes and may limit vascular damage. Thus, we evaluated the response of cryopreserved (Cryop) small (mean diametre = 3mm) arterial allografts (AL) after its implantation in a pig model.
Methods: Two femoral grafts were implanted. Group 1: a fresh autograft (AU) and a fresh AL (n=5). Group 2: a Cryop AU and a Cryop AL (n=5). Group 3: a fresh AL and a Cryop AL (n=5). All animals received Aspirin 500mg/day for three months and cyclosporine A (cyclo) 15-20mgr/Kg/day was given to those in group 3. Then, the animals were euthanized and the implanted grafts were harvested and fixed in formaldehyde. Cross-sections were obtained from the centre of the graft, stained with H-E and orceine for morphometric analyses and immunostained with anti-CD3 antibody to detect T lymphocytes and anti-MAC387 antibody to detect macrophages.
Results: see table. In the ocluded grafts an organized thrombus was observed in the lumen. Infiltration was observed in all AL and absent in all AU. In group 3, Cryop AL had less infiltration than the fresh AL.

	Patency	Luminal stenosis	CD3+MAC387
Fresh AU	5/5 (100%)	17±15%	-
Fresh AL	0/5 (0%)	Occluded	Occluded
Cryop AU	4/4 (100%)	35±17.6%	-
Cryop AL	2/5 (40%)	38.4±29%	+
Fresh AL (cyclo)	4/5 (80%)	22.2±13.1%	++
Cryop AL (cyclo)	5/5 (100%)	61.7±33.4%	+

Conclusions: Cryopreservation increases vascular patency and reduces antigenicity of AL, independently of the presence of intimal hyperplasia and immunosupressive therapy.

CARDIOVASCULAR DISEASE IN WOMEN

P2909 Low serum levels of sex hormone binding globulin are associated with coronary heart disease in postmenopausal women

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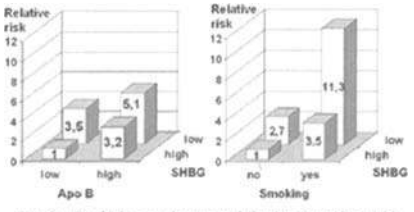
Hyperandrogenemia and low levels of sex hormone binding globulin (SHBG) are frequently found in women with metabolic syndrome which is characterized by low HDL cholesterol (C), hypertriglyceridemia, hyperinsulinemia, and obesity. The contribution of these various factors to coronary heart disease (CHD) is controversial. In a prospective study, coronary angiograms of 87 consecutive postmenopausal women were evaluated using two semiquantitative score systems to estimate the extent of focal and diffuse vessel wall alterations. Fasting sera were analysed for levels of glucose, lipids, insulin, dehydroepiandrosterone sulfate, testosterone, and sex hormone binding globulin (SHBG). Obesity was assessed by body mass index, skinfold thickness and body impedance measurement. After adjustment for age, 55 women with CHD differed significantly from 32 women without CHD by higher levels of LDL-C (159±51 vs. 132±39 mg/dl, p=0.011), apo(lipoprotein) B (121±33 vs. 102±29 mg/dl, p=0.005), triglycerides (115 vs. 91 mg/dl, p=0.02), and basal insulin (7.5 vs. 4.6 mU/l, p=0.016) as well as by lower levels of HDL-C (59.9±18.0 vs. 69.0±17.1 mg/dl, p=0.02), and SHBG (44.6 vs. 68.1 nmol/l, p=0.003). Multivariate analysis by logistic regression identified age (OR 1.22, 95% CI 1.09 to 1.37), smoking (OR 11.46, 95% CI 2.56 to 51.39), SHBG (OR 0.98, 95% CI 0.96 to 0.99), and apo B (OR 1.02, 95% CI 1.01 to 1.04) to be independently associated with the presence of CHD. The relative risk for CHD with these factors is shown in the figure, demonstrating the highest risk for smoking patients with low levels of SHBG. For the first time, low plasma levels of SHBG were found to be associated with coronary heart disease in women independently of insulin, obesity markers, and dyslipidemia.



Cutpoints for „high versus low" were defined by the medians with 47.9 nmol l for SHBG, and 112 mg dl for apo B.

Relative risk for CHD.

P2910 Prothrombotic mutations are associated with increased cardiovascular events in postmenopausal women receiving hormone replacement therapy

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Recent studies have suggested that hormone replacement therapy (HRT) in postmenopausal women (PMW) may be associated with an initial increased cardiovascular risk. Recent reports suggest that the prothrombin variant 20210G to A is associated with an increased risk of events in hypertensive PMW with a previous myocardial infarction. To this end 50 PMW with documented vascular event underwent prospective evaluation of antithrombin III, protein C, free and total protein S, activated protein C resistance, fibrinogen, factor VII:C and homocysteine levels. In all the presence of antiphospholipid antibodies was investigated by kaolin clotting time (KCT), diluted Russel's viper venom time (DRVVT) and by measurement of anticardiolipin antibodies IgG and IgM (ACA-G and ACA-M). Prevalence of factor V Leiden, prothrombin variant G20210A and homozygosity for thermolabile variant C677T of the metilenetetrahydrofolate reductase (MTHFR) were evaluated and compared with those of 50 normal matched controls.

Antithrombin III and protein C were normal in all cases. One patient (2%) showed free protein S deficiency and 3 patients (6%) had activated protein C resistance. Homocysteine levels above 15 μmol/L were found in 3 patients (6%). Antiphospholipids antibodies were found in 35 patients (70%). Among women receiving HRT 87% had combined inherited and acquired prothrombotic factors (OR = 37.3, 95% CI = 8.5-564.3) while no combined prothrombotic factors were found in control PMW receiving HRT.

In conclusion vascular events in women receiving HRT are associated with a high prevalence of combined inherited and acquired prothrombotic factors. Therefore screening for prothrombotic factors may be of help in identify those women at increased risk for cardiovascular events with HRT.

P2911 Myocardial blood flow and flow reserve in response to hormone replacement therapy in postmenopausal women with risk factors for coronary disease

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Estrogen restores endothelium-dependent vasodilation in response to acetylcholine in postmenopausal women, and has a direct, endothelium-independent vasodilatory effect on coronaries. Short-term cyclical hormone replacement therapy (HRT) does not affect maximal myocardial blood flow (MBF) as measured by positron emission tomography (PET). We studied the effects of combined continuous HRT on endothelium-dependent and -independent MBF and myocardial flow reserve (MFR) in postmenopausal women with risk factors for coronary heart disease (CHD).

Methods: We performed dynamic N-13 ammonia PET in 12 postmenopausal women (60±6yrs) to measure MBF and MFR in a 7-month placebo-controlled crossover trial of continuous conjugated equine estrogen (CEE, 0.625 mg/d)/cyclical micronized progesterone (MP, 200 mg/d on days 1-12). All subjects had elevated total and LDL cholesterol levels, and at least one additional CHD risk factor. All had negative dobutamine echocardiograms. MBF was measured using a 3-compartment model at rest, after sympathetic stimulation with the cold-pressor-test (CPT), and after intravenous adenosine (aden) infusion, in order to determine baseline, endothelium-dependent, and endothelium-independent flow, respectively. MFR was measured as the ratio between MBF aden to MBF rest. MBF and MBF normalized to the pressure rate product (PRP) were analyzed. Subjects took HRT and placebo for 3 months each, with a 1-month washout separating phases.

Results: There was no significant difference in overall resting MBF, CPT MBF, aden MBF, or MFR between the baseline values, placebo or HRT treatment arms. We found no significant differences in baseline risk factors, change in risk factors, or medication profile between HRT responders and nonresponders.

	MBF rest	Nrm MBF rest	MBF CPT	Nrm MBF CPT	MBF aden	MFR
Baseline	1.11±0.34	1.10±0.39	0.97±0.29	0.90±0.31	2.53±0.78	2.46±0.98
Placebo	0.85±0.21	0.92±0.25	0.98±0.26	0.97±0.27	2.19±0.75	2.71±1.28
HRT	1.022±0.28	1.14±0.25	0.99±0.36	0.93±0.27	2.34±0.62	2.51±1.10

MBF in ml/g/min; Nrm, normalized.

Conclusions: In this group of healthy postmenopausal women at risk for CHD, HRT does not exert any significant overall effect on endothelium-dependent coronary vascular reactivity or maximal MBF. HRT may not be a successful strategy to improve endothelial function in the primary prevention of coronary heart disease.

P2912 Effects of the hormone replacement therapy on arterial stiffness, blood pressure and angiotensin-converting enzyme plasma levels in postmenopausal healthy women

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In postmenopausal women the incidence of coronary events is increased. The cardioprotective effects of hormone replacement therapy (HRT), observed in primary prevention trials, may in part be due to the effects of estrogens on arterial wall stiffness. Angiotensin-I Converting Enzyme (ACE) is involved in the regulation of vascular tone. It has been suggested that the effects of ACE could be enhaned after the menopausal estrogen's drop.

Methods and Results: Between April 1999 and April 2001, 53 postmenopausal healthy women started HRT under the advice of the gynecologist. At baseline ACE plasma level, Pulse Wave Velocity (PWV) of the carotid-femoral segment and 24-hour ambulatory blood pressure monitoring (ABPM) were assessed. The same determinations were obtained after 6 months of HRT. The results obtained at baseline were: age: 53±4, range 44-61 years; basal ACE level: 28±17, range 3-74 U/L; basal PWV: 10,5±3, range 6-15; and 24-hour ABPM: mean systolic 118±7, mean diastolic 74±6 mmHg. No correlation was found between basal ACE level and basal PWV (r=0.06) or basal ABPM (systolic r=0.1, diastolic r=0.2). Arterial stiffness increased with age (r=0.1), although not significantly (p=0.3).

Six-months follow-up was obtained in 38/53 treated women. No differences were observed between the basal and the follow-up paired data as to: PWV (10,49±2 vs 10,42±2; p=0.8), mean systolic pressure (120±8 vs 121±7; p=0.9) and mean diastolic pressure (78±7 vs 76±7; p=0,7). However, HRT caused a significant reduction of the basal plasma ACE level (28,2±18 vs 19,1±16; p=0.03). To determine whether this ACE-lowering effect of HRT was conditioned by the ACE-gene insertion/deletion (I/D)polymorphism, blood samples from all subjects underwent I/D genotyping by PCR technique. The basal plasma levels of ACE were similarly reduced by HRT independently of the I/D genotypes.

Conclusion Arterial distensibility and blood pressure were not modified by the first six months of HRT, but plasma ACE levels were significantly reduced in this population of healthy women. This indirect intervention on plasma ACE level may be involved in the long-term effect of HRT.

P2913 Postprandial hyperinsulinemia and coronary artery disease among nondiabetic women with metabolic syndrome: a case-control study

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Metabolic syndrome is a typical basis for vascular disease in women. The association between metabolic syndrome and coronary artery disease is complex, and pathways by which the insulin resistant state adversely affects the risk for developing coronary artery disease needs to be elucidated. We planned a case-control study to assess the relation of fasting glucose, fasting insulin, postprandial glucose and postprandial insulin levels with coronary artery disease in nondiabetic women with metabolic syndrome as defined in the National Cholesterol Education Programme Adult Treatment Panel III (ATP III) guidelines.

Among 620 consecutive nondiabetic women screened, 38 with coronary artery disease and metabolic syndrome (42-77 years, mean age 60,6 ± 7) made up the study cohort (group I). Thirty eight age-matched, nondiabetic women with metabolic syndrome but without coronary artery disease (group II), and 38 healthy, age-matched women served as controls (group III, real control group). Demographics, waist circumference, lipids, fasting glucose, postprandial glucose, fasting and postprandial insulin levels were compared among the groups. No differences were identified in terms of prevalences of risk factors between group I and group II. Women with coronary artery disease had higher postprandial insulin level than the women in group II and group III. In reverse stepwise logistic regression analysis postprandial hyperinsulinemia was found to be the single independent determinant for coronary artery disease for women with metabolic syndrome (p=0.02, regression coefficient (RC) per increase by 1 μIU/ml= 1.01, 95% confidence intervall (CI) 1.002 – 1.02 for group I and group II; p<0.0001, RC per increase by 1 μIU/ml= 1.04, 95% CI 1.02-1.06 for group I and group III, respectively).

Our data demonstrate that postprandial hyperinsulinemia is independently associated with coronary artery disease, irrespective of fasting glucose, postprandial glucose, and fasting insulin levels in nondiabetic women with metabolic syndrome.

P2914 Conjugated estrogen administration improves common carotid artery elastic properties in normotensive postmenopausal women

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Improvement in large arteries mechanics may be one of the mechanisms by which estrogen replacement therapy may protect women against cardiovascular disease.

Methods: Towards this end, we investigate the acute effect of conjugated estrogen on the common carotid artery (CCA) elastic properties in 20 normotensive healthy postmenopausal women (age 54±3 years) at baseline and at 20 mins after the intravenous administration of 1.25 mg conjugated estrogen. CCA distensibility was derived by combination of surface ultrasonographic data and simultaneous blood pressure measurements at the brachial artery. The carotid pulsatility index, a measure of brain impedance, was determined electronically by tracing the CCA doppler waveform.

Results: At baseline, CCA distensibility had a negative correlation with both patients' age and time since menopause (r=-0.57 and r=-0.48, $p<0.05$ for both cases). After estrogen administration, estradiol and estrone plasma levels were restored to the range of usual premenopausal values. Estrogen induced a significant increase in CCA distensibility by 0.92±0.005 dyne-1 $cm^2$10-6 (from 2.03 to 2.95 dyne-1 cm^2 10^{-6}) and a significant reduction in CCA pulsatility index by 0.24±0.06(from 2.17 to 1.93)($p<0.001$ for both cases). The improvement of CCA distensibility had a negative correlation with both patients' age and time since menopause(r=-0.46 and r=-0.44, respectively, $p<0.05$ for both cases).

Conclusions: Acute conjugated estrogen administration induced an improvement in CCA elasticity and a reduction in brain impedance in normotensive postmenopausal women. As the womens' age and the time since menopause increased, the improvement in carotid distensibility decreased in such selected subjects.

P2915 The effects of raloxifene and simvastatin on plasma lipids and endothelium

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Raloxifene is a selective estrogen receptor modulator and an attractive alternative to estrogen replacement as it obviates the need for a progestin and does not increase C-reactive protein levels. Statin therapy is the gold standard in the management of hypercholesterolemia.

Methods: We treated 12 postmenopausal women with hypercholesterolemia and coronary artery disease with raloxifene 60 mg/day and simvastatin 20 mg/day in a randomized, double-blind, crossover study. Plasma lipids and cellular adhesion molecules were evaluated and peripheral blood flow studies with venous occlusion plethysmography were performed.

Results: Both simvastatin and raloxifene significantly reduced total and LDL cholesterol compared to baseline values ($p<0.05$) but simvastatin was more effective than raloxifene ($p<0.005$). None of the treatments had any significant effect on HDL cholesterol and triglyceride levels. Only raloxifene significantly reduced Lp(a) and ICAM-1 and VCAM-1 plasma levels compared to baseline (p=0.019, $p<0.0001$ and p=0.003, respectively). Hyperemic blood flow response on raloxifene was significantly higher compared to baseline ($p<0.05$), whereas no significant change was noted on simvastatin. Endothelium independent blood flow induced by nitroglycerine was not influenced by either active treatment.

	Baseline	Simvastatin	Raloxifene
TC (mg/dl)	267±14	176±10*#	231±12*
LDL (mg/dl)	188±12	102±6*#	153±12*
Lp(a)(mg/dl)	35±32	35±10	26±8*
ICAM-1(pg/ml)	175±10	177±11	146±9*
VCAM-1(pg/ml)	553±53	543±72	410±33*

mean±SE, *$p<0.05$ vs baseline, #$p<0.005$ vs raloxifene

Conclusion: Raloxifene administration is associated with lower ICAM-1 and VCAM-1 plasma levels as well as lower Lp(a) levels compared to simvastatin although the latter is more powerful in total and LDL cholesterol reduction. In addition, raloxifene enhances endothelium dependent dilation in the forearm circulation whereas simvastatin does not. Whether these favourable effects of raloxifene on intermediate biologic variables translate into improved clinical outcome, will only be determined when long-term studies are completed.

P2916 Differential effects of gender on large artery elasticity. A study in male to female transsexuals

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Large artery stiffness has been recognized as an independent predictor for cardiovascular events. However, there are not enough data regarding the mechanical behavior of large arteries in relation to gender and particularly to male to female transsexuals.

Methods: Towards this end, we evaluated aortic and carotid elastic properties in 13 male to female transsexuals (age 44±9 years, 18±11 years after surgery) and we compared these findings with those observed in age-matched 10 premenopausal women and 10 men. Aortic and common carotid artery function indices were derived by combination of surface ultrasonographic data and simultaneous blood pressure measurements at the brachial arm. All included subjects had a negative glucose intolerance test.

Results: The three groups of men, women and male to female transsexuals were matched for age (44 vs 42 vs 43 years, respectively) body mass index (25 vs 23 vs 24 Kgr/m^2, respectively), smoking status (current smokers 45% vs 42% vs 48%, respectively), total cholesterol plasma levels (232 vs 229 vs 218 mg/dl, respectively) and office blood pressure (115/75 vs 110/75 vs 115/73 mmHg, respectively)(p=NS for all the above cases). Also, these three groups did not differ regarding the left ventricular echocardiographic data of left ventricular mass (171 vs 142 vs 158 gr, respectively), and relative wall thickness (0.41 vs 0.42 vs 0.41, respectively)(p=NS for all measurements). In contrast, both the aortic and common carotid artery distensibility were significantly lower in men compared to transsexuals (1.6 vs 2.2 dyne-1 $cm^2$10-6 and 1.1 vs 1.8 dyne-1 $cm^2$10-6, respectively, $p<0.001$ for both comparisons) while the aortic and carotid distensibility did not differ between transsexuals and women (2.2 vs 2.3 dyne-1 $cm^2$10-6 and 1.8 vs 1.9 dyne-1 $cm^2$10-6, respectively, p=NS for both comparisons)

Conclusion: These results suggest that vascular adaptations in male to female transsexuals are more closely related to those observed in premenopausal women than to those in age-matched men.

P2917 Ovariectomy changes cardiac and circulating IGF-I in hypertensive Dahl rats

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Background: Multiple epidemiological studies show that heart disease is more prevalent in men than in age-matched women, and experimental studies support that 17b-estradiol (E2) has multiple effects on the cardiovascular system. However, the specific molecular mechanisms that protect women from heart disease are still poorly understood. In this study we analyzed the role of E2 in the development of cardiac hypertrophy in a rat model of hypertension. E2 modulates insulin-like growth factor-I (IGF-I) activity in various cell types, but nothing is known about its effects on the IGF-I system in cardiac cells. As IGF-I is one of the key factors determining cardiac mass, we analyzed changes in IGF-I and IGF-I receptor (R) mRNA in response to ovariectomy in normotensive and hypertensive Dahl rats.

Methods and Results: Nine week old Dahl salt-sensitive (S) and salt-resistant (R) rats were fed a high salt diet (8% NaCl). After four weeks, systolic blood pressure was increased significantly in male and female Dahl S but not in Dahl R rats (127 vs. 190 mm Hg, $P<0.001$). Male rats had higher circulating and left ventricular IGF-I levels than age-matched female rats ($P<0.01$). Hypertensive Dahl S rats have higher cardiac mass and higher cardiac IGF-I mRNA ($P<0.05$ for both), but no difference in circulating IGF-I compared to normotensive SR Dahl rats. Interestingly, ovariectomy abolished the hypertension-induced increase in cardiac IGF-I in females, and at the same time caused a significant increase in circulating IGF-I.

IGF-I in Dahl S and R after ovariectomy

	fem.		ov. fem.		male	
	R	S	R	S	R	S
LV IGF-I	2.9±0.3	5.5±0.8	3.4±0.3	3.6±0.1	8.4±1.0	14.7±3.0
LV IGF-IR	3.4±0.5	3.9±0.2	4.5±0.2	4.2±0.3	3.8±0.2	5.1±0.2
plasma IGF-I	674±22	672±28	978±12	1443±120	853±9	884±23

LV=left ventricle, IGF-IR= IGF-I receptor, ov.=ovariectomy, fem.=female, S=salt sensitive, R=salt resistant

Conclusions: The expression of IGF-I and IGF-IR differs between male and female. E2 modulates levels of cardiac and circulating IGF-I. These effects may contribute to gender-specific mechanisms of hypertrophy, leading to differences in cardiac remodeling.

P2918 Increased CRP levels in women at increased cardiovascular risk predict one year events only when associated with increased interleukin-6 levels

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Elevated CRP levels suggestive of heightened inflammatory state in vascular conditions are often associated with elevated Interleukin-6 (IL-6) levels. It has been suggested that CRP and IL-6 may be a predictors of unfavorable outcome in postmenopausal women (PMW) receiving hormone replacement therapy. Because of the possible metabolic effect of HRT on CRP the relative predictive importance of CRP and IL-6 levels in PMW receiving HRT remains to be elucidated. To this end we evaluated CRP and IL-6 levels before and after initiation of HRT and one year follow up in 346 consecutive PMW (mean age 66±9 years) with cardiovascular risk >20 in 10 years receiving HRT for at least one year.

Overall HRT increased CRP levels by 76% while decreased IL-6 levels by 8%. During 1 year follow up 1 patient died (non cardiac), and 4 had a major cardiovascular event.

PMW with events had elevated CRP levels compared with baseline but within the mean±1SD compared to levels obtained in all women after initiation of HRT. IL-6 levels in PMW with events were significantly higher in PMW with events than in those without events. IL-6 were predictor of future events while elevated CRP levels were associated with an unfavorable outcome only when IL-6 levels were also elevated. In a stepwise multivariate analysis IL-6 levels were a stronger predictor of outcome than CRP. CRP levels were predictors of future events only after removal of IL-6 levels and presence of cardiovascular symptoms from the analysis.

In conclusion CRP levels are increased in PMW receiving HRT. Elevated IL-6 levels may identify those PMW at increased one year risk. CRP levels predict events only when they are coupled with IL-6 levels.

P2919 Does menopausal status alter coronary flow velocity reserve in women with Syndrome X?

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Aim: Syndrome X term is used to describe the patients with typical anginal chest pain, ischaemic exercise tests but normal coronary angiograms. Microvascular dysfunction, measured by reduction in coronary flow velocity reserve (CFR), was speculated to be the major underlying cause. Sex predilection for women, especially around perimenopausal ages, suggests an association between hormonal status and Syndrome X. The aim of this study was to investigate effects of menopause on CFR in women with Syndrome X.

Methods: Women older than 40 years of age with anginal symptoms and positive exercise test results were evaluated with coronary angiographic examination and those with normal coronary angiograms were included in the study. After measuring baseline flow velocity with Doppler flow wire maximum hyperemia was induced by 12-18microgr intracoronary adenosine to determine CFR, defined as the ratio between hyperemic flow velocity/baseline flow velocity in all three epicardial coronary vessels. Women with uncontrolled hypertension, rest angina, hepatic/renal insufficiency, rhythm other than sinus or those using hormone replacement therapy were excluded. The lower limit of normal for CFR was accepted as 2.5.

Results: Thirty-one women with a mean age of 51.6±8.3 years were evaluated for the measurements of CFR. The incidences of CFR<2.5 were 50% for left anterior descending (LAD), 69% for circumflex (Cx) and 37% for right coronary artery (RCA) groups. The study population was subdivided into two depending on the menopausal status. Body mass index, cardiovascular risk profile and exercise capacity characteristics of postmenopausal (n=19) and premenopausal (n=12) women were similar (p>0.05). Postmenopausal women had a significantly higher incidence of angina during exercise tests compared to premenopausal women (74% vs 25%) (p=0.01). The CFR values for LAD and Cx arteries were similar in pre-and postmenopausal groups (2.8±0.6 vs 2.2±1.0, p=0.06 for LAD; 2.2±0.6 vs 2.2±0.9, p=0.5 for Cx), whereas CFR values of the RCA were significantly reduced after menopause (3.2±0.9 vs 2.3±0.5, p=0.001).

Conclusion: Women with syndrome X have an increased incidence of low CFR values, which are more pronounced after menopause, suggesting a role for low estrogen levels in the pathogenesis of this syndrome. This reduction in CFR might have a predilection for the RCA vasculature, the clinical significance of which needs to be clarified.

P2920 Effects of combined hormone replacement therapy on various sensitive systemic markers of inflammation in healthy postmenopausal women

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Atherosclerosis is a chronic inflammatory disease. Several large epidemiological studies suggest a cardioprotective effect of hormone replacement therapy (HRT) in postmenopausal women which might be attributed to a decrease of blood lipids, and improvement of endothelial function, the hemostatic balance and oxidant state. HRT might influence the inflammatory response also. Various trials have shown an increase in C- reactive protein (CRP) serum concentrations and no significant change or even a decrease in fibrinogen concentrations after HRT. The effects of HRT on cytokines and serum amyloid A (SAA) concentration are less well defined.

The aim of the present randomized, placebo-controlled study was to investigate the effects of continuous, combined hormone replacement therapy (HRT) on various markers of inflammation in healthy postmenopausal women.

Sixty-one healthy postmenopausal women (mean age 55.2 ± 8.8 years, duration of menopause 5.8 ± 5.5 years) were randomized to receive a combination of estradiol (2 mg) and norethisterone acetate (1 mg per day) (n=31) or placebo (n=30). Concentrations of high sensitivity CRP, SAA, fibrinogen, interleukin-6 and tumor necrosis factor-alpha (TNF-alpha) were determined before, after 3 and after 6 months of treatment with HRT.

We found a significant increase in concentration of CRP after HRT (median and interquartile range at baseline: 1.12 (0.81-2.06) mg/L; after 3 months 2.64 (1.12-5.06) mg/L and after 6 months 1.95 mg/L (1.34-3.38), all p<0.01 in comparison with baseline). There were no significant changes in the placebo group (1.41 (0.55-2.98) mg/L at baseline, 1.25 (0.66-3.46) mg/L after 3 months and 1.46 (0.54-3.09) mg/L after 6 months). No significant differences were observed for SAA, fibrinogen, interleukin-6 and TNF- alpha between the two groups during the study period.

In conclusion, 6 months of treatment with continuous, combined estradiol and norethisterone acetate increased CRP concentration without significant changes in SAA, fibrinogen, IL-6 and TNF-alpha concentrations in healthy, postmenopausal women. Further studies are needed to explore the clinical relevance of these observations.

P2921 No association between sex hormone levels and coronary artery disease (CAD) in postmenopausal women

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Background: Sex hormones are discussed to influence cardiovascular disease. The aim of the study was to investigate sex hormones in postmenopausal women with angiographically documented CAD.

Methods: 580 postmenopausal women (age > 55 years, FSH > 30 IU/l) scheduled for coronary angiography for clinical reasons were enrolled in LURIC, a prospective cohort study to assess classic and new risk factors for CAD. A detailed history was taken and fasting blood for hormones was obtained. Sex hormones and baseline characteristics were studied for a control group (no stenoses), patients with moderate CAD (stenoses 10-50%) and patients with stenoses > 50%. Women on hormone replacement therapy and digitalis therapy were excluded.

Results: see table.

Postmenopausal women	No CAD, n=132	CAD 10-50% stenoses, n=115	CAD > 50% stenoses, n=333
age (years)	65 ± 6	68 ± 6	70 ± 7*
smoking	21%	22%	37%*
arterial hypertension	58%	74%	74%*
diabetes	19%	29%	41%*
hypercholesterolemia	48%	63%	77%*
LH (IU/l)	30 ± 13	30 ± 13	28 ± 14
FSH (IU/l)	53 ± 23	55 ± 21	49 ± 22*
17-beta-estradiol (ng/ml)	33 ± 35	30 ± 28	32 ± 25
testosterone (µg/l)	0.9 ± 0.9	0.9 ± 1.2	0.8 ± 0.5

* p < 0.005

Conclusion: In postmenopausal women there is no association between sex hormone levels and coronary artery disease. However, the classic risk factors age, smoking, arterial hypertension, diabetes mellitus and hypercholesterolemia are closely associated with presence and extension of CAD.

LIPIDS (EPIDEMIOLOGY)

P2922 Plasma coenzyme Q10 (CoQ10) concentrations in patients with coronary atherosclerosis

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Background: CoQ10 (Ubiquinone) is a fat-soluble vitamin-like substance present in every cell of the body and serves as a coenzyme for several of the key enzymatic steps in the production of energy within the cell. CoQ10 is an important mitochondrial electron transfer component and has been postulated to function as a powerful antioxidant protecting LDL from oxidative damage. CoQ10 as an endogenous antioxidant, packaged into the LDL+VLDL fractions of cholesterol, has been suggested as an important anti-risk factor for the development of atherosclerosis as explained by the oxidative theory. Hence, beneficial effects of supplementation with CoQ have been reported.
Aim: The purpose of this study was to assess which ratio is useful for the risk of atherogenesis in both males and females.
Methods: We performed a case-control study among 30 male and female patients (mean age:55±9) with angiographically documented coronary atherosclerosis (stable or un-stable angina pectoris) and 19 controls (mean age:53±10) free from symptomatic cardiovascular disease and atherosclerotic plaques. Subjects using HMG-CoA reductase inhibitors were excluded from the study. CoQ10 was extracted from plasma by using hexane/methanol and determined by electrochemical method of HPLC.
Plasma CoQ10 concentrations were significantly lower in patients with CAD than in controls. Also, the LDL/CoQ10 ratio was higher in patients with CAD than control. Results are shown on table.

CoQ10 levels and LDL/CoQ10 ratio

	Patients	Control	p
CoQ10 (micromol/L)	0.82±0.43	2.55±1.49	0.003
LDL/CoQ10 (micromol/ml)	169	55.6	0.001

CoQ10: coenzyme Q10, LDL: low density lipoprotein cholesterol.

The positive, significant correlations were found between the total cholesterol/CoQ10 ratio and the HDL/CoQ10 ratio (p=0.02, P=0.342, respectively). The negative correlation was determined between the patients and the controls for total lipids/CoQ10 ratio, the LDL/CoQ10 ratio and the (total cholesterol-LDL)/HDL ratio (p=-0.31, p=-0.12, P=-0.46, respectively).
Conclusion: We concluded that the lower plasma CoQ concentration and the proportion of CoQ10 in lipids available is related to risk of atherosclerosis.

P2923 PPARalpha regulates the secretion and size of VLDL by decreasing the post -ER pre-secretory proteolysis of apoB-100

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The atherogenicity of LDL is determined during the assembly of its pre-cursor VLDL. While large VLDL give rise to small atherogenic LDL with long half life, small VLDL results in less atherogenic LDL with shorter half life. The peroxisome proliferator activated receptor alpha (PPARalpha) has a central role in the lipid metabolism. We have therefore investigate the role of PPARalpha in the assembly and secretion of apoB containing lipoproteins. The PPARalpha agonist WY 14,643 induced an increase in the secretion of apoB-100 but not of apoB-48 in primary rat hepatocytes. The agonist also induced a substantial decrease in the rate of triglyceride biosynthesis and secretion, and a shift from large VLDL to more dens particles banding in the LDL/IDL density range. ApoB-48 VLDL disappeared and was replaced by the "HDL like particle". The PPARalpha agonist increased the co-translational (proteasomal) degradation of both apoB-100 and apoB-48, most likely by lowering the triglyceride biosynthesis. However the agonist decreased the post-ER pre-secretory proteolysis (PERPP) of apoB-100 but not of apoB-48. These results indicate that the increased secretion of apoB-100 was due to a decreased PERPP of the protein. Moreover they demonstrate that PERPP of apoB-100 is actively regulated and not only reflecting the rate of triglyceride biosynthesis. Finally the results imply that apoB-100 and apoB-48 follows different routs during the assembly of VLDL. PPARalpha agonists increased the expression and biosynthesis of liver fatty acid binding protein (LFABP). Transfection of LFABP to McARH7777 cells gave rise to an increased secretion of apoB-100 and apoB-48 and a decrease in the triglyceride biosynthesis and secretion; however the apoB containing lipoproteins remained in the VLDL density range. The increase in the LFABP also gave rise to an increase in mRNA for PPARalpha. This may suggest a mechanism by which in which LFABP and PPARalpha interact to amplify the effect of the PPARalpha agonists on the assembly of VLDL. The proposed mechanism is involved in the regulation of the size of VLDL and could explain the beneficial effects of the lipid lowering fibrates.

P2924 Lipoprotein (a) in coronary atherosclerosis: the impact of age, diabetes and smoking

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Background: Lipoprotein(a) (Lp(a)) is a risk factor for coronary atherosclerosis (CA). Recently, the interactions of Lp(a) with other risk factors and its role in the elderly have attracted much interest. **Methods:** We investigated 535 consecutive patients undergoing coronary angiography. Significant CA was defined as the presence of stenoses of at least 50%. Lp(a) was measured by immunoturbidimetry from fresh serum samples. **Results:** The prevalence (prev.) of significant CA in different risk factor strata is presented in the table. Lp(a) was higher in patients with (n=314) than without (n=221) significant CA (17 vs. 12 mg/dl; p=0.003), and independently predictive of significant CA (controlled for age, gender, hypertension, smoking, triglycerides, HDL-C, LDL-C, and glucose) in multiple logistic regression analysis. Moreover, Lp(a) was lower in patients with (n=123) than without (n=358) diabetes (10 vs. 16 mg/dl; p=0.026), and in patients with (n=316) than without (n=219) a history of smoking (13 vs. 20 mg/dl; p=0.041). Among patients younger than 65 years (n=293) Lp(a) was also an independent predictor for significant CA. Among patients aged 65 years or older (n=242), Lp(a) was not significantly higher in patients with than in those without significant CA (n=147 and n=95; 19 vs. 14 mg/dl; p=0.220).

		Lp(a)	n	prev.			Lp(a)	n	prev.
Diabetes	no	=<30	221	50.2	Smoking	no	=<30	138	52.2
		>30	119	65.5*			>30	81	51.9
	yes	=<30	91	61.5		yes	=<30	219	55.3
		>30	32	71.9*			>30	97	81.4*

*statistically significant versus lowest risk factor stratum; Lp(a) in mg/dl; prevalence (prev.) in %

Conclusions: 1) Lp(a) is elevated in patients with significant CA, but this does not hold true for patients aged 65 years or older. 2) The prevalence of significant CA is highest among patients with both, the conventional risk factors smoking or diabetes and elevated Lp(a) levels. 3) Lp(a) is lower in coronary patients with diabetes or a history of smoking.

P2925 Elevated soluble tumor necrosis factor receptor levels in healthy non-obese adults with the atherogenic dyslipoproteinemia

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Background: Tumor necrosis factor a (TNF-a) expression in human adipocytes and skeletal myocytes correlates with body mass index (BMI), hyperinsulinemia and reduced lipoprotein lipase activity. TNF receptors mediate the cellular actions of TNF-a. In human adipocytes, TNFR2 is the dominant receptor involved in inhibition of insulin signaling. We examine the relationships of select inflammatory mediators in the atherogenic dyslipoproteinemia (ADL) and the effects of statin therapy on select inflammatory mediators. **Methods:** 60 non-smoking, non-obese (BMI <30 kg/m^2), normoglycemic (HbA1c <8%) subjects participating in a randomized 8 week trial comparing pravastatin 40 mg, simvastatin 20 mg, simvastatin 80 mg or placebo. Soluble TNFR1, TNFR2, IL-6 and TNF-a were measured by electroimmunoassay and hs-CRP by immunoturbidimetry. ADL (TG >1.69 mmol/L, HDL-C <1.04 mmol/L in men and <1.30 mmol/L in women, and/or small LDL (< 20.6 nm) was present in 42 subjects. **Results:** ADL subjects were younger (mean±SD; 49±8 vs 54±7 y, p=0.019) and had higher levels of both TNF-a (7.9±18.1 vs 2.1±0.5 pg/mL, p=0.013) and sTNFR2 (3.0±0.6 vs 2.7±0.5 pg/L, p=0.099) compared to the 18 non-ADL subjects. Age and gender predicted ADL (p=0.0436). After adjustment for age and gender, TNF-a, sTNFR1 and sTNFR2 best predicted ADL (Table). There were non-significant age and gender adjusted associations between ADL and IL-6 (p=0.056) and hs-CRP (p=0.093). Statin therapy reduced TNF-a levels more in ADL subjects (7.9±18.1 to 6.2±11.9 pg/mL, p=0.088) than in non-ADL subjects (2.1±0.5 pg/mL to 2.4±0.2 pg/mL, p=0.55), whereas there were no changes in sTNFR1 (p=0.82) or sTNFR2 (p=0.79) in ADL subjects.

Logistic Regression Models with ADL as Outcome	Overall Classification Accuracy (%)	Overall P-value for Model
+ BMI	65.0	0.0842
+ sTNFRS1B	70.0	0.0024
+ sTNFRS1A	61.7	0.0504
+ TNF-a	66.7	0.0471
+ sTNFRS1A + sTNFRS1B + TNF-a + IL-6 + hs-CRP	66.7	0.0372

Age and gender adjusted values.

Conclusions: High TNF-a, sTNFR1 and sTNFR2 levels are markers of the proinflammatory state in ADL. Prospective studies are needed to determine whether elevations in TNF-a, sTNFR1 and sTNFR2 contribute to the development of type 2 diabetes in ADL subjects.

P2926 Dyslipidemia in HIV-infected patients – A new population in coronary risk?

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Introduction: Recent findings suggest that Highly Active Antiretroviral Therapy (HAART) used in HIV-infected patients may cause dyslipidemia (hypercholesterolemia and hypertriglyceridemia) in previous normolipidic patients or aggravate pre-existing hyperlipidemia. Therefore this therapy may contribute to increase the atherogenic potential of these patients and to a possible premature development of coronary disease in this population.
Objective: To compare the lipoprotein profile and the prevalence of hyperlipidemia in the HIV-infected population currently followed in our department of infectious disease (DID) against the same data in the population followed in DID before the introduction of HAART with Protease Inhibitors (PI) in the treatment of this disease.
Population and Methods: The HAART with PI began, in our hospital, after January of 1997.
We studied - as pre-HAART population (A) - every patient followed in DID in 1996 (n=81), mean age 33 years (range 19-56), 58 males. As post-HAART population (B) - were studied the patients being followed in DID by September of 2001 (n=425), mean age 35 years (range 20-77), 343 males.
We compared the mean values of total cholesterol and triglycerides of both populations and evaluated the prevalence of hypercholesterolemia and hypertriglyceridemia.
Results: The mean cholesterol level in the pre-HAART population (A) was 155,2 mg/dl and 182,5 mg/dl in B. The mean triglyceridemia was 151,9 mg/dl in A and 144,2 mg/dl in B. The prevalence of hypercholesterolemia, defined as cholesterolemia > 200 mg/dl was 18,3% (n=15) in A and 31,1% (n=132) in B (p=0,019). The prevalence of hypertriglyceridemia defined as triglyceridemia > 200 mg/dl was 22,2% (n=18) in A and 13,6% (n=58) in B (p=0,048).
Conclusions: Despite the sample limitations, a tendency to a change in the lipoprotein profile of the HIV-infected population is found. Besides the trend towards a decrease of the mean values of triglyceridemia - possibly justified by a better control of the virus (which has hypertriglyceridemic effect) - there is a clear raise of hypercholesterolemia after half-decade of HAART. As a possible consequence, we may expect a future increase of coronary disease incidence in these patients.

P2927 Association of risk factors of coronary artery disease and clot strength

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Purpose: The clot strength (the elastic shear modulus of clotting blood) is increased in patients with coronary artery disease. Elevated plasma levels of fibrinogen, C-reactive protein (CRP), homocysteine and cholesterol are also associated with increased risk of coronary artery disease. The aim of our study was to investigate the association of plasma concentrations of these risk markers with clot strength.
Methods: After obtaining informed consent, 81 subjects were included: 20 healthy volunteers, 23 with stable angina, 19 with unstable angina (UA) and 19 with myocardial infarction (MI). Upon admission, blood was drawn from the UA and MI patients before any antithrombotic treatment. Clot strength in dyne/cm^2 was measured on citrated whole blood by thrombelastography. Plasma concentrations of fibrinogen, CRP, homocysteine and total cholesterol were correlated to clot strength using Spearman's correlation coefficient.
Results: A highly significant correlation was observed between fibrinogen concentration and clot strength ($r = 0.82$, $p < 0.0001$). Clot strength was also logarithmically associated with the CRP level ($r = 0.54$, $p < 0.0001$). There was no correlation between cholesterol level and clot strength ($r = -0.12$, p ns), or homocysteine level and clot strength ($r = 0.1$, p ns).
Conclusion: Clot strength is directly correlated to the level of plasma fibrinogen, the structural component of the blood clot. The association between clot strength and CRP level follows a logarithmic pattern. The clinical application of the latter finding requires further investigation. Increased plasma levels of homocysteine and total cholesterol have no direct effect on clot strength.

P2928 Risk of coronary artery disease associated with thrombin activable fibrinolysis inhibitor (TAFI) levels

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Introduction: Thrombin activable fibrinolysis inhibitor (TAFI) is a recently described component that potently inhibits t-PA-induced fibrinolysis. High TAFI levels may lead to an hipofibrinolytic state contributive to an increased risk of arterial thrombotic disease. To our knowledge,there is no available information about TAFI functional levels in coronary artery disease (CAD).
Aim of the study was to analyze the risk of arterial thrombosis related to TAFI.
Material and methods: TAFI antigenic (Ag) and functional (Fn) levels in plasma of 104 CAD patients were compared to those of 150 control subjects. The Ag levels were determined by an ELISA method (Hyphen, Andrésy France) whereas Fn was measured by Mosnier methodology. Thrombotic risk was calculated by logistic regression (odds ratio and confidence interval 95% CI). Cut-off points were calculated by ROC. Results are expressed as mean ± SD.
Results: All conventional cardiovascular risk factors (age, hypertension, smoking, familial history of CAD, obesity, diabetes mellitus) as well as Factor VIIIc and fibrinogen were significantly more prevalent in CAD than in controls, but heterozigous for the PT20210A and Factor V mutations were not. Furthermore, no differences in TAFI Ag levels were found between CAD patients (107%±28) and controls (106%±31). However, TAFI Fn was increased ($p<.001$) in CAD patients (116.2%±24.3) compared to controls (101%±19). To calculate the risk we compared patients with TAFIf levels higher than 120% (n=39)vs controls (n=14). Unadjusted OR was 5,8(95%CI 3-11,5)for patients with CAD compared with controls. Adjusted OR by age, sex, smoking,diabetes,hypertension, family history of arterial disease, fibrinogen, factor VIIIc and atrial fibrilation (AF), AAF, FVL and PT20210A did not change, and showed an increased risk of 5,6 (95%CI2-16,2)for CAD patients compared with controls.
Conclusions: Elevated TAFI Fn levels are associated with a higher risk of CAD. Therefore, inhibition of t-PA-induced fibrinolysis may play an important role in pathogenesis of CAD and also may have important therapeutical implications. Determination of TAFI Fn levels is, nowadays, more specific than antigenic.

P2929 Atrial fibrillation is independently associated with raised plasma von Willebrand factor in women but not men: results from the Rotterdam study

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Introduction: Atrial fibrillation (AF) is associated with increased risk of stroke. Elevated prothrombotic plasma markers have been demonstrated in AF, but may be due to additional underlying cardiovascular disease, rather than AF itself. We sought to confirm the presence of independent associations between AF and three prothrombotic markers in a large, community-based study of an elderly population.
Methods: We measured plasma von Willebrand factor (vWf, a marker of endothelial damage/dysfunction), fibrinogen and soluble P-selectin (sP-sel, a marker of platelet activation) in 162 patients with AF and 324 age and sex matched paired controls participating in the Rotterdam Study.
Results: Amongst the group as a whole (51%male; mean age 77,sd8), there were no significant differences in plasma fibrinogen (p=0.8), sP-sel (p=0.6) or vWf (p=0.08) between cases and controls. However, AF was significantly associated with increased vWf amongst women (146 vs. 136iU/dl,p=0.02), but not men (142 vs. 141iU/dl,p=0.8). After adjusting for potential confounding factors using conditional logistic regression analysis, a significant independent relationship remained between vWf and AF in women (OR=1.19, 95%CI 1.02-1.40, table), with a fivefold increase in risk of AF in the upper quartile of vWf compared to the lower quartile (OR=5.0,95%CI 1.34-18.7).

Odd Ratio for Atrial Fibrillation (per 10iU/dl Increase in Plasma von Willebrand Factor Levels) Among Gender Groups

		Odds Ratio (95% confidence interval)
Whole Group (n=486)	Crude	1.06 (0.99-1.12)
	Adjusted	1.06 (0.98-1.15)
Men (n=249)	Crude	1.01 (0.93-1.10)
	Adjusted	1.00 (0.90-1.12)
Women (n=237)	Crude	1.11 (1.01-1.26)
	Adjusted	1.19 (1.02-1.40)

Conclusion: Amongst an elderly community-based population there was no significant relationship between AF and plasma fibrinogen or sP-sel levels. However, AF was independently associated with increased plasma vWf among women but not men. The relationship between AF and vWf (endothelial damage/dysfunction) deserves further investigation as a potential mechanism of the increased risk of stroke in elderly women with AF.

P2930 Generation velocity of small-sized platelet aggregates predicts thrombotic complications during percutaneous coronary interventions

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Background The ischemic complications of percutaneous coronary interventions (PCI) including abrupt closure, side branch occlusion or distal embolization of platelet aggregates or thrombus deteriorate the effects of the treatment. Generation velocity of small-sized platelet aggregates monitored by a novel laser-light scattering method is a sensitive marker of platelet activation. The method is quite useful because data are obtained at bedside in about 15 min.
Methods and Results: We measured ADP-induced platelet aggregability in platelet-rich plasma obtained from the peripheral vein in patients with acute coronary syndromes (ACS) (n=60) prior to urgent PCI to predict ischemic complications during the procedures. Platelet aggregability in stable exertional angina (SEA, n=54) was also measured as control. Platelet aggregability was determined as generation velocity of small-sized platelet aggregates which contain 70-1,400 platelets by a novel platelet aggregometer with a laser-light scattering method. Small-sized platelet aggregates (counts/ 10sec) were generated more frequently in ACS than in SEA ($26.53x10^3 \pm 5.19x10^3$ vs $14.52x10^3 \pm 2.54x10^3$, $p<0.05$). There were no differences in medium- (1,000-11,000 platelets) and large-sized (11,000-33,000 platelets) aggregates between the two groups. Periprocedural ischemic complications occurred in 15 patients (EVENT group) of the 60 ACS patients underwent PCI. Generation of small-sized aggregates was elevated in the EVENT group than in non-EVENT group (n=45) ($60.46x10^3 \pm 13.16x10^3$ vs $15.22x10^3 \pm 3.58x10^3$, $p<0.0001$). Logistic regression analysis revealed that the peak velocity of the generation of small-sized aggregates predicts ischemic complications during PCI procedures ($p=0.0093$, $R=0.325$) Meanwhile other coronary risk factors, antiplatelet or anticoagulant agents used and balloon to reference vessel diameter ratio had no predictive values.
Conclusions Monitoring of platelet aggregability measured by the laser-scattering method prior to PCI is informative and useful to predict periprocedural thrombotic complications in patients with ACS.

P2931 Clotting factor VIII is a key player for plasmatic and in situ thrombosis in chronic thromboembolic pulmonary hypertension

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Background: Chronic thromboembolic pulmonary hypertension (CTEPH) may be considered as an extreme variant of recurrent thromboembolism. However, no abnormalities of coagulation and fibrinolysis have been defined that explain the clinically progressive thrombosis in the pulmonary vasculature of these patients.
Methods and Results: Because plasma factor VIII (FVIII) levels above 230IU/dl have been shown to confer a 6.6-fold increased risk for recurrent deep venous thrombosis, we measured plasma FVIII levels in CTEPH patients (n=111). FVIII in CTEPH patients (232.9±103.2%) was higher than in age and sex matched healthy controls (93.0±23.3%, $p<0.001$, n=82) and patients with non-thromboembolic pulmonary hypertension (PAH, 168.2±81.2%, p=0.009, n=77). Hemodynamic improvement after pulmonary thromboendarterectomy (PTE) did not normalize plasma FVIII levels (226.4±88% versus 212±94%, p=0.8999, n=22). To substantiate the genetic background of this observation in CTEPH patients, blood group analyses were performed. Blood group non-O was more prevalent in CTEPH patients (82%) than in PAH patients (56%) or the Middle European population (60%, p=0.0026). RT-PCR demonstrated FVIII expression in CTEPH pulmonary thrombi harvested during PTE and in freshly excised deep leg vein thrombi. In situ-hybridization showed FVIII mRNA in endothelial cells and smooth muscle cells within organized CTEPH pulmonary thromboemboli and deep leg vein thrombi, which displayed identical histological patterns.
Conclusions: The data support the concept that elevated plasma FVIII is a key player and not an epiphenomenon in the pathogenesis of CTEPH. In addition, local FVIII expression may promote thrombus organization and recurrence.

CARDIAC REHABILITATION

P2932 Diastolic augmentation is an independent predictor of improved outcome in 3536 patients following enhanced external counter pulsation (EECP)

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Background: EECP produces diastolic augmentation of coronary blood flow and has been shown to improve angina. Despite this it has only recently been used in Europe for treatment of refractory angina. We analysed the clinical characteristics, degree of diastolic augmentation and response to treatment in patients enrolled in the international EECP patient registery (IEPR) in America (US) and Europe. **Methods:** 3536 patients underwent a course of treatment consisting of 35 one-hour sessions. Canadian class (CC) of angina was carefully documented pre- and post the 7 week course. Diastolic augmentation was assessed using a finger plethysmogram. The ratio of the peak diastolic amplitude to peak systolic amplitude was calculated. **Results:** There was a significant difference in baseline characteristics between groups. The US group (3465 patients) had more diabetic (43 vs 22.9% p=<0.001), hypertensive (71.6 vs 31% p=<0.001), hyperlipidaemic (81.1 vs 64.3% p=<0.001) patients, and more patients with multi-vessel disease (76.2 vs 62.5% p= <0.05) as well as more patients in CC III/IV (86.6 VS 54.9% P=<0.01). The European group (71 patients) had more patients who had previously undergone CABG (93 VS 70.9% P=<0.001), but fewer PTCAs (23.2 vs 66.3% p= <0.001) and more male patients (91.5 vs 75% p= <0.001). Despite these differences logistic regression analysis showed no difference in outcome between the two groups. However diastolic augmentation (measured as the last peak ratio) was an independent predictor of outcome in both patients with modest angina (CC I/II, odds ratio 1.67 [1.19 - 2.34]) and patients with severe angina (CC III/IV, odds ratio 1.63,[1.38 - 1.92]). Diabetes, smoking, hypertension, prior CABG, female sex and increasing age were all associated with lower levels of diastolic augmentation and diabetes (0.68 [0.41 - 0.96]), CABG (0.54 [0.35 - 0.82]), and heart failure (0.71 [0.59 - 0.85]) with a poorer outcome. **Conclusion:** The patients in the European and US EECP registries vary in their baseline characteristics. Despite this diastolic augmentation remains an independent predictor of benefit offering a possible physiological rationale for the improvement in symptoms seen in these patients.

P2933 How to advise on return to work after myocardial infarction or heart surgery

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Background: Current advice on return-to-work is based on stress testing and ejection fraction. Neither correlate well with prolonged work capacity. Recommendations derived from work physiology state that mean workload should not exceed 33% and peak workload should not exceed 50% of maximal aerobic power. **Objective:** To determine whether simple heart rate recording while at work combined with detailed job description is feasible and could help in advising patients on return-to-work on short and long term. **Methods:** We included 54 patients referred to our tertiary centre after an acute myocardial infarction or heart surgery to assess if they could resume work. All underwent regular bicycle stress testing. They were evaluated while at work for the duration of a full work shift. A continuous heart rate recording was performed with a Polar sports-tester and was analysed with commercially available software. Simultaneously a detailed report of the various tasks and working conditions was made. Workload was calculated using the measurements obtained during bicycle stress test and Polar recording. If the mean workload exceeded 33% and/or repeated peak loads exceeded 50% of maximal aerobic power and considering specific job requirements we advised people not to resume their previous job but to look for job adaptation or to stop working. If not, return-to-work was encouraged. One-year follow-up to inform on their current working situation was done by phone or a house call. **Results:** A total of 54 patients, (47men/7 women, mean age: 49 years), were examined. 25(46%) were advised to resume their previous job and 29(54%) were advised to look for job adaptation or to stop working. Patients for whom no objection was made to resume work had lower mean and peak workload registrations. There were no differences in age, gender, cardiac risk factors, and ejection fraction or total bicycle workload. Of those advised to resume their previous job, 20(80%) did; 14(16%) returned to work under adapted working conditions and 1(4%) stopped working claiming that it was physically to demanding. After 1 year 23(92%) of those patients were doing the same job as before the cardiac event. Of the remaining 29 patients advised to look for job adaptation or to stop working, 14(48%)obtained a job adaptation, 7(24%) stopped working and 8(28%) maintained their previous work. After 1 year 22(76%) had either adapted or stopped working. **Conclusion:** An on-the-job Polar registration in combination with extensive job description is easy-to-use and valuable in advising on return-to-work on short and long term.

P2934 Mental stress-induced ischaemia in patients after myocardial infarction

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Background: Myocardial ischemia may be triggered by exercise and non-exercise stimuli.The purpose of this study was to determine the usefulness of laboratory mental stress (MS) in inducing myocardial ischemia and/or cardiac arrhythmia in patients (pts) post myocardial infarction, with stable coronary artery disease.
Methods: Sixty four men, mean age 45 ± 6 years underwent: 15 min mental stress test during 24 h Holter monitoring and exercise stress testing.
Results: Only 8 pts (13%) had positive mental stress test (MS(+)). Five of them had ST segment depression > 1.0 mm (STD), and the remaining 3 pts had cardiac arrhythmias (2 pts had nonsustained VT, 1 pt had episode of FA). All episodes were silent. MS(+) pts had higher heart rate (HR) during the mental test than those with negative stress test (MS(-)) (120/min vs 105/min, $p< 0.05$). In contrast, at least one episode of daily life ischemia (DLI) was recorded in 23 pts (36%) on Holter monitoring. In MS(+) pts average duration of DLI (17 min vs 10.5 min, $p<0.05$) and mean HR during ischemia (124/min vs 94/min, $p< 0.05$) were greater than in MS(-) pts.
Exercise – induced ischemia (STD > 1.0 mm) was observed in 29 of 64 pts (45%). However, in MS(+) pts exercise duration (708 ± 132 s vs 924 ± 174 s, $p< 0.01$), time to 1 mm STD (432 ± 108 s vs 624 ±162 s, $p< 0.01$) were significantly shorter and double product at 1mm STD (13400 ± 2913 vs 14800 ± 3321 mmHg/min, $p< 0.05$) was lower than in MS(-) pts.
MS(+) pts become less accurate during mental work in comparison to MS(-) pts. Intelligence level was comparable in both groups [43.2 in MS(+) pts vs 40.2 in MS(-) pts; NS].
Conclusion: 1. Mental stress – induced ischemia is a weak inducer of ischemia and arrhythmia in patients with stable coronary artery disease.
2. Patients with mental stress – induced ischemia are more likely to display ischemia during daily life and exercise stress testing.
3. Only subset of patients after myocardial infarction, with specific psychological profile, is prone to ischemia and arrhythmia during mental work.

P2935 Effect of physical training on quality of life and exercise tolerance in patients with chronic heart failure

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Aim: To assess changes in quality of life (QoL) and oxygen consumption in the course of two different patterns of physical training in patients with congestive heart failure (CHF).
Material and Method: The study population consisted of 42 men, age 55.9 ± 8.1 years with ischaemic CHF (NYHA II and III), and a duration of CHF 3.1 ± 1.0 years, receiving standard pharmacotherapy. Patients were randomised into groups: A (14 men) - with constant level of workload, B (14 men) - with progressive/increasing level of workload and C (14 men) not trained and serving as controls. In groups A and B physical training was conducted for up to 6 months (60 min of training daily, 3 times a week). Mean age, BMI, duration and severity of CHF were similar in all groups. QoL was assessed three times: at the beginning of the study and at 3 and 6 months by using the Minnesota Living with Heart Failure Questionnaire (MLHF). At the start and at six months of training in all patients cardiopulmonary exercise test and echocardiography were performed.
Results: Oxygen consumption as well as exercise time and workload (in METs) improved in both trained groups ($p<0.01$). Improvement in QoL was positively correlated with peak VO2 only in group B ($r=0.47$, $p<0.05$). At baseline as well as at 6 months no significant differences between groups in left ventricular systolic and diastolic function were found. At the start of the study, the MLHF total indexes were similar in groups A and B, but lower than in group C, i.e. 65.4, 65.3 and 71.0 points respectively. In groups A and B improvement in the MLHF score was observed ($p<0.001$) at 3 and 6 months. However, overall improvement in MLHF was markedly greater in group B (39%) than in group A (29%) ($p<0.01$), as well as oxygen uptake (VO2 max in group increased B from 15.3 to 19.3 ml/kg/min and VO2 max in group A from 15.4 to 16.5 ml/kg/min, $p<0.001$).
Conclusions: Regular physical training improves QoL in men with CHF, but only progressive/increasing workload seems to markedly improve oxygen uptake.

P2936 Gender differences in physical health and psychological well-being at entry into rehabilitation after acute myocardial infarction

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Objective: To identify gender differences at the beginning of cardiac rehabilitation that may influence the long-term outcome of myocardial infarction.
Methods: Study subjects were 309 men and 201 women, aged 30 to 75, who were admitted to a cardiac rehabilitation clinic about three weeks after first acute myocardial infarction. At baseline, all patients completed a standardized interview that included a number of questions on socio-economic factors, chronic diseases, and subjective well-being. To assess symptoms of anxiety and depression the Hospital Anxiety and Depression Scale (HADS) was introduced at the beginning and the end of the four-week clinic stay.
Results: After adjustment for age, a number of statistically significant sex differences were found. Women reported significantly more co morbid conditions such as high blood pressure, angina pectoris, gall bladder disease, kidney disease and osteoporosis. They also reported more somatic symptoms such as weakness, sleeplessness and back pain. The age-adjusted prevalence of high anxiety scores (HADS > 10) was 23% in women and 13% in men ($p < 0.05$). And about 16% of women compared to 8% of men were identified as depressed. In age-specific analyses, the gender differences were more pronounced in younger patients (under 60 years) than in older patients (60 to 75 years). Applying multivariate analyses, among men and women it was found that the prevalence of chronic somatic diseases was the best predictor for the occurrence of anxiety and symptoms of depression. After 4 weeks of in-hospital rehabilitation both men and women reported significantly less symptoms of anxiety and depression though the gender differences in anxiety remained significant.
Conclusion: The results of this study indicate that age and gender specific plans of care need to be directed at patients with coronary heart disease.

P2937 Clinical predictors of return to work in coronary artery bypass surgery patients – Data from the PERISCOP study

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Background: PERISCOP is a prospective multicentre study aiming at the determination of prognostic factors by non invasive methods after coronary artery bypass surgery (CABG).
Aim: to analyse the predictors of return to work (RTW) in the subgroup of patients (pts.) aged less than 60 yrs, working before CABG.
Methods: Pts. with recent (20 days) CABG were prospectively included in this study (41 rehabilitation centers). Cardiac evaluation was performed at 20±10 days after CABG by exercise testing, echocardiography and 24-hour ambulatory ECG monitoring (AECG). Clinical status and RTW were evaluated by self-administered questionnaire one year after surgery. A logistic regression using RTW (yes=1) as the dependent variable was used to identify the independent predictors of work resumption.
Results: Among the 2065 pts. included in the PERISCOP study, 530 pts. (male: 95%, mean age: 50.5 ± 6 yrs) met the inclusion criteria. Among them, 26 were lost to follow up and 340 (68%) returned to work. The median delay before RTW was 3 months. The significant predictors of RTW are shown on table.

table

Variable	Increase in risk of not returning to work (CI)	p value
Age (> 51)	64% (77-45)	< 0.0001
Occupation (worker)	50% (74-5)	0.033
Region (South East)	72% (86-42)	0.0005
Angina	59% (80-15)	0.016
Dyspnea	53% (72-21)	0.0041
Exercise duration < 7min	46% (65-16)	0.0063

Conclusions: In a representative sample of French pts. experiencing recent CABG, increased age, severity of disease, low occupational category and living in the South-East of France were predictors of low rate of RTW after surgery.

P2938 Short term multidisciplinary cardiac rehabilitation program improves endothelial function

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Background: Individual risk factor modification, in particular lipid lowering, has been shown to improve endothelial function in CAD patients. However, little is known about the effect of comprehensive risk factor modification and lifestyle change on endothelial function.
Goals: To assess the effect of a 3 month multidisciplinary cardiac rehabilitation program (CR) on endothelial function in stable CAD patients.
Methods: 42 stable CAD pts (7%women), mean age 65y were randomized into CR group (n=21) and no-CR group (n=21), who received usual care. CR program included: exercise (EX) training, nutritional counselling, lipid lowering medication and lifestyle modification.
Endothelial-dependent brachial artery flow-mediated vasodilation (FMD) was assessed with high resolution (10MHz) ultrasound at baseline, and after 1, 2 and 3 months. Lipids and EX testing Bruce protocol were assessed at baseline and at 3 months.
Results: Baseline characteristics were similar in both groups, including FMD. Compared to no-CR group, at the end of the 3rd month, CR patients had significantly reduced TC, LDL, TG ($p<0.02$), increased EX test duration ($p=0.02$). and increased weekly EX time (4.8±0.8 hours vs 0.5±1 hours in the control group, $p<0.0001$). BMI did not change in either group. In the CR group a trend towards improved FMD (%) was detected after 2 months (8.1±7 vs 4.9±6 at baseline), which became statistically significant at the 3rd month (10.5±6, $p=0.009$ compared to baseline, and $p=0.04$ vs no CR group) (Table). No change in FMD was detected in the control group over the study period.

Endothelial Function (FMD%)

FMD (%):	Baseline	Month 1	Month 2	Month 3
CR Group	4.9±6	4.8±7	8.1±7*	10.5±6**$
no-CR group	6.2±8	3.6±9	3.5±7	5.7±8

*p=0.055 Vs. no-CR group, **p=0.009 Vs.baseline CR, $p=0.04 Vs. no-CR

Multivariate analysis revealed a non-linear association between LDL change, weekly EX and %FMD response.
Conclusions: 1) CR significantly improved lipid profile, EX duration and weekly EX. 2) Endothelial function significantly improved in the CR group at the end of 3months. 3) LDL change and weekly EX hours are associated with this improvement.

P2939 Changing clinical patterns in the cardiac rehabilitation program, the Haifa experience

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Today's cardiology patients are likely to be older, sicker, and to stay in hospital fewer days than in the past. Most of them undergo treatment modalities such as angioplasty and stenting, thus, being diagnosed, treated and discharged quickly.
To evalute the impact of changing clinical trends on cardiac rehabilitation trends we have assessed retrospectively 4159 files of patients joining rehabilitation program during the period 1.5.83-31.12.01.
Clinical & demographic data were retrospectively assessed at 3 time points, 1984, 1993, and 2001.Data reviewed included: age,gender, socio-economic status, early drop-out rates, risk factors, F.C., previous infarction, percutaneous interventions (PCI's), CABG,pacemaker or valve surgery, primary/secondary prevention.Medications were reviewed as well.
Results: mean age increased constantly, 59.4 years± 4.5, 67± 5.8 and 71.5±4.9, $p<0.01$, gender distribution did't change through the years (females 20.5%, 23.1%, and 21%, p=ns); pensioners = 27%, 43.7%,and 47.5% respectively, $p<0.01$. "Blue Collars" = 58%, 51.6%, and 44.5%, $p<0.01$).Early drop-out(less than 6weeks of participation)=20.4%, 18.7%, and 20.5%, p=ns.
Previous myocardial infarction = 91%, 72.4%, and 71%,p=0.05; previous PTCA/Stent=0%, 8.4%, and 63.1%, $p<0.01$, F.C. II-III = 2.6%, 4.5%, and 17.5%, $P<0.01$. Participation for primary prevention = 6.5%, 8.1%, and 5.9%, p=ns.Medications: Aspirin = 64.8%, 70.5%, and 92.5%, $p<0.01$, Statins = 4.6%, 30.5%, and 56.1%, $p<0.01$, Beta blockers = 21.9%, 25.4%, and 48.1%, $p<0.01$.
Conclusions = participants mean age increased consistently over the years. In 1984 most patients joined rehabilitation program following myocardial infarction while in 2001 most were patients who underwent CABG and/or percutaneous interventions. Use of Aspirin, Statins and beta blockers grew consistently. Cardiac rehabilitation constitutes a high fidelity mirror of the changing clinical trends and patterns in cardiology.

P2940 Improved physical performance and circulatory response in moderate to severe heart failure patients undergoing exercise training

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Background: Determination of hemodynamic outcome in patients with congestive heart failure (CHF) undergoing cardiac rehabilitation has been difficult to assess due to lack of easily obtainable hemodynamic information in every day practice. Thoracic electrical bioimpedance (TEB) relies on the proportional change in the conduction of alternating current applied across the thorax as a function of blood volume in the heart and great vessels. Using this technique cardiac index (CI) can easily be determined. The aim of our study was to assess the functional responses and immediate post peak exercise CI obtained non-invasively using TEB in patients with moderate to severe CHF before and after participating in cardiac rehabilitation program.
Methods: Between 01/2000 and 08/2001 57 consecutive patients with moderate to severe CHF (FC III) who were referred to a cardiac rehabilitation program were studied. Among those, 44 patients, mean EF=24±5% (exercise group) participated in the exercise program, and 13 patients, mean EF=21±7%, did not (control group). Six minute walk test, Modified Bruce exercise test duration and immediate post peak exercise CI, obtained by TEB, were measured before and after 18 weeks physical training.
Results: The 2 groups did not differ in age, gender, risk factors, prevalence of ischemic etiology and treatment. No differences were found between exercise and control in all measured parameters before physical training: six minute walk test, Modified Bruce exercise test duration and immediate post peak exercise CI (310±87 vs. 306±108meter, 5.8±.6 vs. 4.4±3.6 minutes, and 4.1±1.2 vs. 4.4±1.3 L/min/m^2, respectively).Significant differences were found between groups after 18 weeks of physical training in all parameters: six minute walk test, Modified Bruce exercise test duration and immediate post peak exercise CI (444±84 vs. 281±127 meters, $p<0.001$, 9.8±3.0 vs. 4.1±3.7 minutes, $p<0.001$, and 4.8±1.0 vs. 3.6±1.3L/min/m^2, $p=0.0053$, respectively)
Conclusions: Exercise training improves immediate post peak exercise cardiac index, detected by thoracic electrical bioimpedance, in moderate to severe heart failure patients (FC III). This improvement can partially contribute to the better physical performance detected in these patients after physical training.

BRAIN NATRIURETIC PEPTIDE IN HEART FAILURE MANAGEMENT

P2941 N-terminal pro-brain natriuretic peptide accurately predicts heart failure in general population. A population study

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Background: Plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are raised in left ventricular dysfunction (LVD). Population studies looking to predict heart failure (HF) were performed using BNP however NT-proBNP was never used in a multicenter study. In this multicenter population study we compared NT-proBNP in high NYHA class subjects with NYHA class I.
Methods: We studied 215 subjects (119 F, 96 M), age 66±9, (45-86), obtained from a random sample of 432 people from the Valencian Community, (Alicante, Castellon, Valencia), that in a previous questionnaire declared to suffer from some degree of dyspnea. These 432 subjects were referred to their local hospital (10 hospitals involved in the study) where blood samples were taken, an echo-Doppler study was performed, a specific questionnaire was completed and were classified according to NYHA functional classes. All blood samples were sent to the same hospital and NT-proBNP was measured. Out of the 432 subjects we got a positive answer from 215.
Results: NT-proBNP was significantly lower, 53 (0-1860) pg/ml in NYHA I than in NYHA>1, 132 (13-2585), $p<0.0001$. Receiver operator characteristic (ROC) curves which plot sensitivity vs 1-specificity of the ability of NT-proBNP to separate NYHA I from NYHA>I, had an area under the curve (AUC) of 0.74. At a cut-point of 85 pg/ml there was a 73% sensitivity, 66% specificity in detecting the presence of NYHA>I. When we compared gender groups (male, M; female, F) we found an AUC in F of 0.74. At a cut-point of 85 pg/ml there was a 74% sensitivity, 60% specificity in detecting the presence of NYHA>I, when compared with ROC curve in M, AUC 0.8, 71% sensitivity, 75% specificity at a cut-point of 88 pg/ml in detecting the presence of NYHA>I.
Conclusions: This multicenter population study shows that an easy, rapid test can predict HF. We believe that NT-proBNP may be a good screening tool for detecting HF in general population.

P2942 B-type natriuretic peptide predicts sudden death in patients with chronic heart failure: a selection mode for ICD implantation?

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Background: Given the high incidence of sudden death in patients with chronic heart failure (CHF) and the efficacy of implantible cardioverter defibrillators, an appropriate tool for prediction of sudden death is desirable. B-type natriuretic peptide (BNP) has prognostic significance in CHF and the stimuli for its production also cause electrophysiological abnormalities. This study tests BNP levels as predictor of sudden death.
Methods: BNP levels, in addition to other neurohormonal, clinical and hemodynamic variables, were obtained from 452 patients with LVEF <35%. For prediction of sudden death only survivors without HTx or mechanical assist device and patients who died sudden were analysed.
Results: Up to 3 years 293 patients survived without HTx or mechanical assist device, 89 patients died and 65 patients unterwent HTx. Mode of death was sudden in 44 patients (49%), pump failure in 31 patients (35%), 14 patients (16%) died from other causes. Univariate risk factors of sudden death were log BNP (x2=12, p=0.0005), log N-ANP (x2=9, p=0.003), LVEF (x2=8, p=0.005), log N-BNP (x2=8, p=0.006), systolic blood pressure (x2=6, p=0.01), big endothelin (x2=5, p=0.03), NYHA class (x2=4, p=0.04) and diastolic blood pressure (x2=4, p<0.05). In the multivariate model log BNP levels were the only independent predictor of sudden death (x2=12, p=0.0005). Using a cutpoint of log BNP <2.11 (=130 fmol/ml) Kaplan Meier sudden death free survival rates were significantly higher in patients below (99%) compared to patients above this cutpoint (81%) (p=0.0001).
Conclusion: BNP levels are a strong independent predictor of sudden death in patients with CHF.

P2943 Brain natriuretic peptide kinetics during dynamic exercise in patients with chronic heart failure

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Background: Plasma levels of brain natriuretic peptide (BNP) are increased in patients (pts) with chronic heart failure (CHF) and left ventricular dysfunction. Previous reports demonstrated that dynamic exercise stimulates BNP secretion in CHF. However, little is known about the kinetics of BNP secretion during dynamic exercise and the following recovery phase in a larger cohort of CHF pts.
Methods: We prospectively studied 37 pts with CHF (60 ± 10 years, 9 women, LVEF 26 ± 6%) and 20 healthy controls (58 ± 11 years, 6 women, LVEF 60 ± 3%). All CHF pts had a LVEF < 35%. Cardiopulmonary exercise testing was performed in all CHF pts and controls. BNP (pg/ml; immunoassay, Biosite Diagnostics, San Diego, USA) was obtained prior to symptom-limited bicycle exercise, at peak exercise and at 1 and 5 minutes of recovery time.
Results: Peak VO2 was significantly higher in controls than in CHF pts (19.8 ± 4.1 vs. 15.0 ± 3.6 ml/min/kg, p < 0.01). BNP concentrations were significantly higher in CHF pts compared to controls at rest, peak exercise and at 1 and 5 minutes of recovery. In controls BNP-levels were not significantly different at rest (25 ± 20 pg/ml), peak exercise (35 ± 31 pg/ml, n.s.) or in the recovery phase (41 ± 40 and 38 ± 36 pg/ml, n.s.). In CHF there was an increase of BNP from rest (428 ± 421 pg/ml) to peak exercise (507 ± 450 pg/ml, n.s.), 1 minute (560 ± 460 pg/ml, n.s.) and 5 minutes recovery (526 ± 424 pg/ml, n.s.). Interestingly, six of 37 CHF pts (16%) showed a decrease in BNP at exercise compared to rest but none of the controls. These CHF pts with a decrease in BNP showed no difference in peakVO2, LVEF and BNP at rest, but a significant difference in BNP at peak exercise (202 ± 241 vs. 555 ± 465 pg/ml, p < 0.05) when compared to pts with an BNP increase at exercise.
Conclusions: During dynamic exercise BNP levels rise from rest to a maximum at 1 minute recovery phase. However, BNP levels at peak exercise and at recovery are not significantly different compared to BNP at rest. This is due to the fact that in contrast to controls there are some CHF patients with a decrease in BNP at exercise. The reason for this phenomenon deserves further study.

P2944 Comparison of a near patient NT-ANP test with plasma NT-ANP and BNP for the detection of left ventricular systolic dysfunction in suspected heart failure

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Background: The natriuretic peptides BNP (brain natriuretic peptide) and NT-ANP (atrial) are useful in the evaluation of patients with suspected LV systolic dysfunction (LVSD). Near patient natriuretic peptide tests would allow a more rapid and convenient assessment of the breathless patient, particularly in primary care.
Methods: We evaluated a near patient spot-test for NT-ANP in 53 patients with suspected heart failure, comparing with plasma BNP (direct IRMA) and NT-ANP (RIA). Echocardiography was performed and wall motion score calculated (9 segment). Sensitivity, specificity, negative and positive predictive values were calculated for the detection of moderate-severe LVSD (WMSI less than 1.3) and milder LVSD (WMSI less than 1.6).
Results:

WMSI13	sensitivity(%)	specificity (%)	PPV (%)	NPV (%)
ANP spot-test	83.3	35.3	27.8	87.6
ANP 4.0ng/ml	91.7	41.2	31.8	94.3
BNP 50pg/ml	100	37.3	32.3	100
WMSI16				
ANP spot-test	87.5	37.9	53.5	78.1
ANP 4.0ng/ml	83.3	51	58.1	78.6
BNP 50pg/ml	93.7	44.8	58	90.0

BNP, NT-ANP and the spot-test were all significantly higher (p<0.05) in patients with LVSD. BNP correlated most strongly with WMSI (r = -0.404). 16 of 17 false positive spot-tests had elevated BNPs. 10 of these had another echo abnormality present: significant valve dysfunction, LVH or right heart dilatation.
Conclusions: Near patient testing of NT-ANP is feasible and of similar diagnostic value as plasma NT-ANP in patients with suspected heart failure. BNP is superior to both in terms of ability to exclude the presence of LVSD.

P2945 A comparison of BNP and NT-proBNP as markers of mild forms of left ventricular dysfunction

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Introduction: It has been shown that among all hormones secreted upon ventricular stretch, B-type natriuretic peptide (BNP) has emerged as the best biochemical diagnostic marker for heart failure (HF). However, NT-proBNP appears to be a useful new marker. We therefore tested, whether NT-proBNP can effectively diagnose mild heart failure.
Methods: After giving informed consent 86 consecutive patients (31-83 years) with clinically suspected mild HF who were referred for coronary angiography were enrolled in this study. BNP was measured within 2 hours from blood collection in EDTA-whole blood samples by a POCT immunoassay (TRIAGE®, Biosite Diagnostics, La Jolla, CA). For NT-proBNP plasma samples were stored at -20 °C until batch measurement by an enzymeimmunoassay (Biomedica, Vienna, Austria). 47 persons showed to have a normal LVEF and were referred as controls. 19 patients presented with mild systolic heart failure, and 20 patients suffered from isolated left ventricular diastolic dysfunction.
Results: NT-proBNP concentration was significantly increased in patients with mild heart failure (p=0.002, median: 425.95 fmol/ml) compared to control persons (median: 217.5 fmol/ml), but there was no significant difference between controls and patients with isolated diastolic heart failure. BNP concentrations were significantly increased in patients with mild heart failure (p=0.00) or isolated diastolic dysfunction (p=0.018). Receiver-operating characteristic (ROC) plot analysis showed an equal performance for BNP and NT-proBNP in the discrimination between controls and patients with mild heart failure. The area under curve (AUC) was 0.78 ± 0.065 for BNP and 0.75 ± 0.076 for NT-proBNP. A BNP of <46 pg/ml or a NT-proBNP of <249 fmol/ml ruled out mild heart failure with a negative predictive value of 0.9 or 0.83, respectively. However, BNP was the better diagnosic marker to determine patients with isolated diastolic dysfunction with an AUC of 0.7 ± 0.065 vs. the AUC of NT-proBNP of 0.49 ± 0.079. Moreover, the inverse correlation with angiographically determined LVEF was better for BNP (r=-0.395, p<0.01) than for NT-proBNP (r=-0.273, p<0.05).
Conclusion: The diagnostic performance to correctly select patients with isolated diastolic dysfunction was significantly increased with BNP. However, NT-proBNP may be an equal useful biochemical marker as BNP for the diagnosis of mild heart failure.

P2946 BNP variations under diuretic treatment predicts short term mortality in acute or decompensated heart failure

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Hospitalisations for decompensated heart failure are linked with bad outcome. We wanted to determine if BNP plasma level at the admission or the variations of BNP plasma levels in the first 24 hours of treatment could help to determine the immediate outcome of the patients and could help to monitor the effects of the diuretic treatment.

Background Treatment of decompensated heart failure is currently based on clinical criteria. BNP is an hormone correlated to left ventricular end diastolic pressure. We hypothesize that measuring BNP levels might be useful in assessing short term outcome in patients hospitalised for decompensated heart failure.

Methods We have included 120 consecutive patients hospitalised for decompensated heart failure and we have measured BNP levels at the admission and 24 Hours later.

Results A BNP plasma level at the admission > to 1200 pg/ml is linked with an in hospital mortality of 70%. All the patients with a good outcome despite initial BNP > 1200 pg/ml showed a dramatic decrease of their BNP levels in the first 24 hours of treatment.

Conclusions In patients admitted for decompensated CHF, Initial BNP plasma level and changes in the first 24 hours are very strong predictors of in hospital mortality.

P2947 Is the viral infection influencing the cardiac BNP concentration in DCM patients?

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Dilated cardiomyopathy (DCM) is one of the most frequent causes of heart failure however its pathogenesis is not well understood. There is growing body of evidence suggesting that viral infection and autoimmunologic mechanisms may also play an important role in the pathogenesis of both DCM and a predisposing condition, acute myocarditis (MC). Thus, identifying the factors that regulate these processes is of prime importance in understanding the etiology of these diseases.

Brain natriuretic peptide (BNP) is secreted in an endocrine fashion mainly from the heart in response to ventricular stretch, and produces several biological effects. Although, increased BNP levels are used as a prognostic marker in patients with heart failure and acute coronary disease, the molecular mechanisms that lead to abnormal regulation of BNP remain unknown. Thus, the aim of the study was to evaluate the pattern of cardiac BNP concentrations in different groups of DCM and their diagnostic and/or predictive potency. The study was performed in the following group of patients: 1- Control (EF>50%), n=11; 2- DCM, virus negative, without inflammation, n=9; 3- DCM, virus negative, inflammation positive, n=9; 4- DCM, virus positive, without inflammation, n=10; 5- DCM, virus positive, inflammation positive, n= 9; 6- No DCM, no MC, virus negative, without inflammation, EF<50%, n=10. Endomyocardial biopsies were taken from the right ventricular septum with a cordis bioptome. The samples were homogenised and extracts assayed for BNP levels in duplicate by immunoradiometric assay (IRMA; Schering, Germany).

We observed an increase in BNP concentration in biopsies of all patients groups compared to the control group (group1: 30 ± 11; group 2: 235 ± 140; group 3: 234 ± 86;. group 4: 119 ± 57; group 5: 48 ± 13; group 6: 74 ± 42 pg/mg protein). However, these increases were more pronounced in groups without the virus (group 2 and 3) compared to the groups with virus (group 4 and 5)

To our knowledge, this is the first report demonstrating the measurement of BNP concentrations in single endomyocardial biopsies with a wet weight of 3 to 5 mg. Surprisingly, the BNP concentrations are significantly reduced in DCM with viral infection and/or inflammation compared to virus and inflammation negative DCM. Whereas a direct viral control on BNP seems to be unlikely, the possible explanation for this observation is that inflammatory cells and factors released by viral infection could influence BNP generation and release.

P2948 N-terminal pro brain natriuretic peptide as a prognostic marker in the general population

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Background: The purpose of the study was to evaluate N-terminal pro brain natriuretic peptide (NT-proBNP) as a marker for cardiac morbidity and all-cause mortality in the general population.

Methods: Randomly selected subjects (382 women & 290 men) in 4 age groups (50-59 (n=174); 60-69 (n=204); 70-79 (n=174); >80 years (n=120)) from four Copenhagen general practitioners filled in a heart failure questionnaire, were examined clinically, and by ECG, echocardiography and NT-proBNP measurements.

Results: Median (range) follow-up was 805 (60-1171) days. In Cox proportional hazards analyses, age, gender, history of hypertension, history of ischaemic heart disease, diabetes, dyspnea, ankle edema, heart rate, systolic and diastolic blood pressures, abnormal ECG, left ventricular ejection fraction (LVEF) and NT-proBNP were evaluated as potential prognostic markers for mortality, congestive heart failure (CHF) admissions and other cardiac admissions. Log10(NT-proBNP) (hazard ratio (HR)=5.70, p<0.0001) and male gender (HR=3.10, p=0.004) were independent markers for mortality. Log10(NT-proBNP) (HR=13.8, p<0.0001), dyspnea (HR=1.45, p=0.003) and male gender (HR=2.71, p=0.03) were independent markers for CHF admissions, and log10(NT-proBNP) (HR=3.69, p<0.0001), abnormal ECG (HR=2.56, p=0.003) and history of ischaemic heart disease (HR=1.90, p=0.03) were independent markers for other cardiac admissions. All-cause mortality (26 vs 6 deaths, p=0.0003), first CHF admissions (18 vs 2, p=0.0002), and first admissions from other cardiac causes (44 vs 13, p=0.0001) were significantly higher in subjects with NT-proBNP>32.5pmol/l (study median) than in subjects with NT-proBNP<32.5pmol/l.

Conclusion: In this large sample of the general population, NT-proBNP was identified as the single most powerful prognostic marker for all-cause mortality as well as for cardiac morbidity. The results point towards an increased role for NT-proBNP analysis in the evaluation of patients suspected of heart failure.

P2949 Comparison of NT-proBNP and NT-proANP in the prediction of mortality and heart failure after acute myocardial infarction

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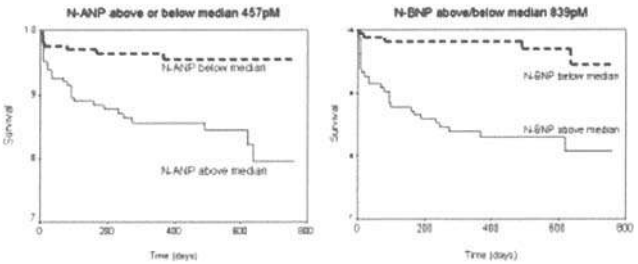
The N-terminal fragments of both B-type (N-BNP) and atrial(N-ANP) natriuretic peptide are useful in the prediction of LV function and mortality after acute MI(AMI).Few studies have directly compared the prognostic utility of N-ANP with N-BNP.Plasma N-ANP and N-BNP were measured on day three in 327 unselected patients following AMI (152 anterior; 245 male,median age 65[range 32-95]). During a follow up of median 472 days(range 5-764),33(10.1%) patients died, 70 were hospitalised with an ACS(21.4%),19(5.8%) with LVF,and 43(13.1%) suffered outpatient LVF. Median N-ANP and N-BNP were higher in patients with any of previous MI, angina, LVF or diabetes (all p<0.05). N-BNP was higher in anterior AMI (1252 v 708 pM,p=0.004). Both peptides increased with worsening Killip class (p=0.0005),and with the degree of LV dysfunction (p<=0.001) assessed by echo.In univariate analyses, both N-ANP and N-BNP were higher in those dying, readmitted with heart failure or developing outpatient LVF (all p=0.0005).Factors significant in univariate analysis (previous MI,angina,age,N-ANP,N-BNP,1/creatinine and Killip Class for death) were entered into multivariate regression models. Only N-BNP remained independently predictive of all three endpoints (odds ratios: death 3.6[1.4- 9.3], admission with LVF 11.0[2.1-56.7] and outpatient LVF 2.4[1.0-5.5]. N-ANP failed to have additional predictive value over N-BNP. Survival was lower in those with N-ANP(p=0.0004) or N-BNP(p=0.0001) above the median (see Fig 1).



Cox proportional hazards models for death showed significant ratios for only N-BNP(5.0[CI 2.0-12.9]). A single measure of N-BNP following AMI independently predicts death and heart failure, and is superior to N-ANP in this respect.

P2950 Automated measurement of N-terminal proBNP for biochemical detection of left ventricular dysfunction

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N-terminal pro-brain natriuretic peptide (proBNP), the amino-terminal signal peptide of the second cardiac natriuretic peptide BNP has been found a promising biochemical marker of left ventricular (LV) dysfunction and heart failure (CHF).
In the current study, we aimed to assess for the first time the usefulness of fully automated measurement of proBNP (Elecsys®proBNP, Roche Diagnostics). A total of 467 subjects late after myocardial infarction (MI, MONICA MI register Augsburg; elapsed time after MI 1-10 years, mean 5.6) as well as 458 siblings without MI were studied. All study subjects were characterized with respect to hemodynamic and anthropometric parameters and renal function (glomerular filtration rate, GFR) and underwent echocardiography with respect to LV ejection fraction (EF, Simpson method) and mass (Devereux method). In subjects with MI, proBNP was significantly increased (299.3±29.1 pg/mL vs. no MI 84.9±7.7, $p<0.01$), particularly in the presence of LV dysfunction (515.5±142.8 pg/mL, $p<0.01$ vs. no MI), LV hypertrophy (447.9±73.0 pg/mL vs. MI without hypertrophy 264.2±31.9, $p<0.03$), renal dysfunction (456.3±72.1 pg/mL vs. MI without renal dysfunction 221.5±13.3, $p<0.01$), and CHF (340.9±36.2 pg/mL, $p<0.01$ vs. no MI). In uni- and multivariate analyses, a significant correlation was present between proBNP and EF (r: -0.20, $p<0.001$), LV mass index (r: 0.27, $p<0.001$), and GFR (r: -0.27, $p<0.001$) in addition to age (r: 0.14, $p<0.001$) and gender (β-coefficient 70.3±33.2, $p<0.04$ multivariate). Patients with LV dysfunction (EF<35%) were detected by proBNP with a sensitivity of 91% and specificity of 75% at an optimal cutpoint of 188pg/mL and an area under the ROC curve of 0.85.
ProBNP represents a novel diagnostic tool for the detection of LV dysfunction in patients at risk. Automated measurement of this marker is now feasible and may provide clinical benefit. In addition to LV dysfunction, increased LV mass, female gender, and renal dysfunction should be considered as important confounders of increased proBNP concentrations.

P2951 BNP and risk stratification in patients with congestive heart failure

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We sought to determine the possible relationship among brain natriuretic peptide (BNP) and cardiopulmonary parameters commonly used for risk stratification in patients suffering from congestive heart failure (CHF-PTS).
Fourty, II and III NYHA class, consecutive CHF-PTS of various etiology were enrolled; mean age was 70,9 ± 11.6; the mean ejection fraction (EF) was 32,9% ± 8.3.
BNP plasma level was measured by means of the triage system (Biosite Diagnostics, Triage BNP test) before cardiopulmonary test (CPx). CPx parameters were: VO2 peak (PVO2), anaerobic threshold (AT), ventilation and carbon dioxide production ratio (VE/VCO2), ventilation and breathed out oxygen ratio (VE/VO2)and percent of maximum predicted PVO2 (%PVO2). The measured parameters are shown in the the table.

BNP	263.6 ± 258.9
AT	9.56 ± 2.2
PVO2	12.35 ± 4.3
% PVO2	60.1 ± 20.3
VE/VO2	47.85 ± 11.9
VE/VCO2	38.14 ± 8.2

A reverse statistically significant correlation among BNP level, AT (r=-0.82), PVO2 (r=-0.80) and % PVO2 (r=-0.60) was observed.
Although PVO2 is an important measurement in predicting survival from heart failure, CPx is not a simple technique and is not widely available. Our preliminary data suggest that bedside BNP measurement can be considered an useful substitute of a complex test as the CPx for risk stratification.

P2952 N-terminal pro-brain natriuretic peptide: relationship to peak oxygen consumption and cardiac power output in patients with chronic heart failure

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N-Terminal pro-Brain Natriuretic Peptide (N-BNP), the 76 amino acid residue amino terminal portion of pro-BNP, has previously been shown to independently predict left ventricular function and 2 year survival in patients with CHF. N-BNP also provides a strong correlation with reduced left ventricular wall motion index on echocardiography. We examined the relationship between N-BNP and other indicators of left ventricular dysfunction determined by exercise testing in patients with CHF.
We recruited 86 patients with CHF (mean age 56 years, 84% male, mean LVEF 36.8±2%) and 10 healthy controls (mean age 52 years, 90% male) to undergo cardiopulmonary exercise testing with measurement of peak oxygen consumption (VO2) and haemodynamic variables such as peak cardiac power output (CPO), an independent predictor of prognosis. A venous blood sample was taken and plasma N-BNP was measured using an in-house non-competitive two site immunoluminometric assay for full length N-BNP.
We demonstrated significantly higher N-BNP (expressed as mean±SEM) levels in the CHF group (905±173 fmol/ml) compared with the control group (26.7±12 fmol/ml, $p<0.0001$). There was a significant negative correlation of log N-BNP with both peak VO2 ($r = -0.5$, $p<0.0001$) and peak CPO ($r = -0.572$, $p<0.005$) in the group with CHF. N-BNP and exercise parameters did not show any significant relationship in healthy controls.
We have shown plasma levels of N-BNP to significantly correlate with peak VO2 and peak CPO, both strong predictors of prognosis in CHF.

P2953 The efficacy of new interventional programmes depends on the stage of heart failure, evaluated by BNP plasma concentration

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Background: Interventional programmes, including heart failure (HF) outpatient clinics and HF nurse specialists improve life quality, reduce readmission rates and decrease costs. Little is known in which stage of disease such interventions are most effective. Therefore, we evaluated the impact of severity of HF, determined by BNP plasma levels, on the efficacy of special outpatient care ("SOPC") in comparison with conventional outpatient care ("COPC").
Methods: 112 HF patients (mean age: 68±12 years, 63% males) who were hospitalized 3 months prior to study entrance were randomized to SOPC (n=48) or COPC (n=64). In all patients an individual prescription of RAAS antagonists and additional betablockade including an uptitration schedule according to the ESC guidelines was performed by a cardiologist at the first visit in the HF outpatient clinic. Diuretic regimes and additional therapies (digitalis, anticoagulants, antiarrhythmics) were prescribed as clinical appropriate. In the SOPC group regular home visits by a nurse specialist were arranged after 3, 6 and 12 months as well as in case of worsening HF to controll the precribed therapeutic regimen, body weight, heart rate, blood pressure and signs and symptoms of HF.
Results: In the SOPC group a significant reduction of the event rate (readmission rate and all cause mortality) was achieved (17% vs. 33%; p=0.04). BNP plasma levels were comparable in both groups (314±272 vs. 369±369 pg/ml; p=n.s.). Patients with BNP values <260 pg/ml had a comparable 1 year event-rate, with and without SOPC (0% vs. 3%; p=n.s.). Patients with BNP values >260 pg/ml, treated with SOPC had more events compared to patients with BNP values <260 pg/ml treated with COPC (32% vs. 3%; p=0.002). Patients with BNP values >260 pg/ml had fever events with SOPC than with COPC (32% vs. 75%; p=0.003).
Conclusion: The efficacy of SOPC depends on the severity of disease evaluated by BNP levels. BNP determination might be helpful in selecting patients for novel care programmes, especially when resources are limited.

P2954 Influence of additional restrictive filling patterns on N-terminal pro-brain natriuretic peptide in patients with systolic dysfunction

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Background: In patients with congestive heart failure (CHF) natriuretic peptides have been reported to improve risk assessment. The aim of the present study was to investigate whether in CHF patients with a systolic dysfunction (LVEF < 40%) an additional restrictive diastolic left ventricular dysfunction affects N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations.
Methods: Plasma concentrations of NT-proBNP were measured by ELISA in 296 CHF patients (age 59 ± 11 years, 84% male, n = 82 ischemic, n = 214 dilated cardiomyopathy, n = 37 NYHA functional class I, n = 120 class II, n = 139 class III, LVEF 22 ± 10% and peak oxygen uptake 14.7 ± 5.5 ml/min/kg). Doppler echocardiographic transmitral flow patterns revealed additional restrictive (E/A > 2 or E/A 1-2 and DT < 140 ms) filling patterns in 177 patients. Non-restrictive patterns were defined as E/A < 1 or E/A = 1-2 with DT > 140 ms.
Results: In patients with additional restrictive filling patterns (RF) plasma levels of NT-proBNP were twice as high (524 ± 555 vs. 216 ± 263 pmol/l; p < 0.001) than in patients with non-restrictive filling patterns (NRF). During a follow-up period of 31 ± 18 months 79 patients were admitted to hospital due to cardiac decompensation, 87 patients died due to cardiac causes. Compared to patients without cardiac event, patients with cardiac decompensation had significantly higher NT-proBNP concentrations (312 ± 446 vs. 473 ± 453 pmol/l; p = 0.009). There were also significant differences between survivors and non-survivors (320 ± 413 vs. 614 ± 626 pmol/l; p = 0.003).
Even after stratification into two groups (patients with non-restrictive filling patterns (NRF) and patients with additional restrictive filling patterns (NRF)) significant differences between the groups of patients without cardiac event and patients with cardiac decompensation (NRF: 178 ± 244 vs. 488 ± 576 pmol/l, p < 0.001; RF: 321 ± 291 vs. 586 ± 520 pmol/l, p = 0.009) and between the groups of survivors and non-survivors (NRF: 178 ± 211 vs. 388 ± 386 pmol/l, p < 0.001; RF: 301 ± 320 vs. 590 ± 622 pmol/l, p = 0.001) could still be detected.
Conclusion: Patients with systolic dysfunction and additional restrictive filling patterns have significantly increased concentrations of NT-proBNP compared to patients with non-restrictive diastolic dysfunction. However, even within each subgroup NT-proBNP predicted cardiac decompensation and cardiac death, indicating that its predictive value is not simply explained by discriminating restrictive and nonrestrictive diastolic dysfunction.

P2955 Brain natriuretic peptide in the diagnosis of systolic left ventricular dysfunction in Chagas disease

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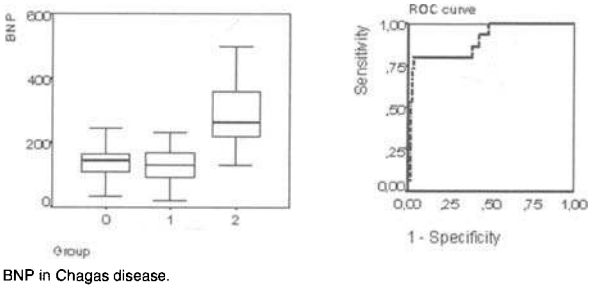
Background: Left ventricular (LV) dysfunction is the main predictor of mortality in Chagas disease,a major health challenge in Latin America. It would be desirable to develop screening methods to indicate which patients should be submitted to complete echocardiographic LV evaluation.
Objective: To describe the behavior of brain natriuretic peptide (BNP) in a cohort of Chagas disease patients in order to establish its diagnostic value in the detection of LV global systolic dysfunction.
Methods: Chagas disease patients and healthy controls without other diseases were submitted to a standardized protocol, including ECG and echocardiography. They were divided into three groups according to serological status and LV ejection fraction (LVEF): group 0 (controls, n = 26), group 1 (Chagas disease, LVEF > 0.40, n = 136) and group 2 (Chagas disease, LVEF < 0.41, n = 15). BNP plasma concentrations were measured using radioimmunoassay. The diagnostic performance of the BNP values in the diagnosis of LV systolic dysfunction in the Chagas disease population was evaluated using the ROC curve.
Results: BNP concentrations were significantly elevated in group 2 when compared to group 1 and controls and are correlated with LVEF (rs: - 0.46, P < 0.01). The area under the ROC curve for various concentrations of BNP in the diagnosis of LV dysfunction was 0.89 ± 0.04. An elevated BNP (>210 pg/dl) has a sensitivity of 80%, specificity of 93.2%, positive predictive value of 52.2% and negative predictive value of 98.1%.
Conclusion: This study discloses a hitherto unrecognized elevation of BNP values in Chagas disease patients with global LV systolic dysfunction. BNP measurement can be an accurate test in the screening of patients who are at high risk of heart failure and death.



BNP in Chagas disease.

P2956 Does left ventricular geometry influence the concentration of plasma brain natriuretic peptide in patients with congestive heart failure?

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A restrictive pattern of the transmitral flow which is a marker of increased left ventricular (LV) filling pressure has been shown to be associated with elevated plasma brain natriuretic peptide (BNP) in patients with congestive heart failure. However, little is known about the implication of LV geometry in this setting. We hypothetized that LV dilation should also contribute to increased plasma BNP levels through an increased in LV mass and LV stress.
We studied 187 heart failure patients with LV systolic dysfunction (LV ejection fraction < 45%), who underwent a complete echocardiographic study and a plasma BNP measurement (RIA). Patients were divided in subgroups according to the presence of a restrictive (R: E/A ratio > 2 or 1<E/A ratio < 2 and deceleration time of E < 130 ms) or non restrictive (nR: E/A ratio < 1 or 1<E/A ratio < 2 and deceleration time of E > 130 ms) pattern of the transmitral flow and to the degree of LV dilation (LV end diastolic diameter, LVEDD > or < median value, 67 mm).
The highest plasma BNP concentration was found in the subgroup of patients with both restrictive pattern and LV dilation (table).

	A: nR and LVEDD < 67 mm, n=59	B: nR and LVEDD > 67 mm, n=39	C: R and LVEDD < 67 mm, n=45	D: R and LVEDD > 67 mm, n=44
Plasma BNP (pg/ml)	94±112	159±180	165±192	281±190

Group A, B, C: NS, A versus D, p = 0.00002, B versus D, p= 0.013; C versus D, p = 0.015

Multiple regression analysis shows that LVEDD (beta 0.18), E/A ratio (beta 0.31) and LV ejection fraction (beta -0.32) were independently associated with plasma BNP.
We conclude that LV geometry independently influences the increase of plasma BNP in patients with chronic heart failure.

P2957 N-terminal pro-brain natriuretic peptide and hypertension. Its importance in the diagnosis of heart failure

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Background: Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) may be useful in the diagnosis of heart failure (CHF) and asymptomatic ventricular dysfunction (LVD) and its increase has a relationship with wall stress (WS). A frequent cause of the increase in WS is hypertension (HT). In a population study we compared NT-proBNP levels in subjects with and without the diagnosis of HT.
Methods: We studied 215 subjects (119 F, 96 M), age 66±9, (45-86), obtained from a random sample of 432 people from the Valencian Community (Alicante, Castellon, Valencia), who in a previous questionnaire declared to suffer from some degree of dyspnea. These 432 subjects were referred to their local hospital (10 hospitals were involved in the study) where blood samples were taken, an echo-Doppler study was performed, a specific questionnaire was completed which included the question asking if they had been previously diagnosed with HT. Blood samples were all measured independently at the same hospital. Out of the 432 subjects we got a positive answer from 215 and this study was complete in 202. Seventy two subjects declared that they had been previously diagnosed with HT and 130 had not been diagnosed with HT. NT-proBNP levels are in pg/ml and mitral flow propagation velocity (Vp) in cm/s.
Results: For the whole population NT-proBNP was 88 (0-2585). When we compared HT subjects, LV mass index 126±44 gr/m^2, Vp=57±19, with no HT, LV mass index 106±46 gr/m^2, Vp=60±19, we found higher NT-proBNP levels in HT, n=72, 123 (0-2184) when compared with no HT, n=130, 77 (0-2585), $p<0.01$. When we excluded systolic LVD we found 118 (0-2184) in HT and 72 (0-997) in those without HT, $p<0.01$. When we also excluded diastolic LVD we found 101 (0-430) in HT and 69 (0-997) in those without HT, $p<0.05$.
Conclusion: This population study shows that hypertension must be take into account when using NT-proBNP for CHF diagnostic with and without systolic LVD and independently from the detection or non-detection of diastolic LVD. This should be confirmed in new studies for its potential importance in clinical practice.

P2958 Brain natriuretic peptide for the evaluation of dyspnoeic patients in the emergency department

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Dyspnea is a common symptom in a general emergency department. While some dyspnoeic patients should quickly be referred to a cardiologist, others show diseases that are non-cardiac. Brain natriuretic peptide (BNP) is a well known serologic marker for determination left ventricular dysfunction. Thus, we examined wether by determination of BNP Patients with cardiac diseases can be divided from Patients with non-cardiac diseases.
Method: We measured BNP in 100 patients with dyspnea as leading symptom in the emergency department. Treating physicians were blinded to BNP measurements. Afterwards all patients were divided into "cardiac" and "non-cardiac" patients by a panel blinded to BNP results. This was done on the basis of all findings gathered during the patient's hospital stay. The severity of dyspnoea was evaluated by a standardized Scoring system. Groups were compared
Results: The table shows the results.

	BNP	Dyspnoea-Score
Cardiac (n= 57)	905,0 fmol/l	87,5
Non-cardiac (n= 43)	83,5 fmol/l	84
p-value	<0,0001	n.s.

Conclusion: BNP proves to be an excellent marker in the emergency department. Dyspnoe related to ventricular dysfunction can be divided from "non-cardiac"-dyspnea within 20 minutes. Measurements of BNP should be incorporated of the diagnostic work-up of dyspnea in the emergency department.

P2959 What are the N-terminal pro-brain natriuretic peptide values in normal subjects? A community-based study

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Background: Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) may be useful in de diagnosis of heart failure (CHF) and asymptomatic ventricular (LV) dysfunction. However the range of NT-proBNP observed in subjects without cardiovascular (CV) disease or LV dysfunction are poorly defined and may be age specific.
Methods: We studied 215 subjects (119 F, 96 M), age 66±9, (45-86), obtained from a random sample of 432 people from the Valencian Community, Spain (Alicante, Castellon, Valencia), who in a previous questionnaire declared to suffer from some degree of dyspnea. These 432 subjects were referred to their local hospital (10 hospitals were involved in the study) where blood samples were taken, an echo-Doppler study was performed, a specific questionnaire was completed and subjects were classified according to NYHA functional classes. Tapes were all measured independently at the same hospital. Out of the 432 subjects we got a positive answer from 215. From this population, we identified subjects in sinus rhythm without CV, renal or pulmonary disease or diabetes, they were not on any CV medications, and they all had a normal systolic, diastolic and valvular function on Echo (n=88). NT-proBNP levels are in pg/ml.
Results: For the whole population values of NT-proBNP were 47 (0-318). When we compared age groups (50-60, AI; 60-70, AII and 70-80, AIII) we found $p<0.001$. We found a higher NT-proBNP in AII subjects, 69 (0-291), when compared with NT-proBNP in AI subjects, 27 (0-127), $p<0.05$. NT-proBNP was also higher in AIII subjects, 81 (16-318), $p<0.0001$.
Conclusion: This multicenter population study shows that in absence of disease or abnormal cardiac structure or function, the effect of age on NT-proBNP values may need to be taken into consideration when using NT-proBNP in clinical practice.

P2960 Brain natriuretic peptide levels in assessment of left ventricular dysfunction in type 2 asymptomatic diabetic patients

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Background: Diabetes is associated with an increased risk for cardiovascular disease including increased left ventricular mass and wall thickness, reduced left ventricular systolic chamber. Echocardiography is the basis for diagnosis of left ventricular (LV) dysfunction, but its cost and availability limits its use for routine screening. As Brain Natriuretic Peptide (BNP) accurately reflects early LV dysfunction, we hypothesized that BNP might be useful as a prospective screening tool in asymptomatic diabetic patients to evaluate LV function prior to perform echocardiography.
Methods and Results: Among 121 type 2 asymptomatic diabetic patients, consecutively hospitalized for the assessment of diabetic status, 81 patients having both BNP and complete echocardiography were studied. BNP was measured in EDTA-whole blood by a point-of-care immunoassay (Triage®, Biosite Diagnostic, BMD, France). The results were blinded to the cardiologist making the assessment of LV diastolic dysfunction or LV systolic dysfunction. According to echographic data, patients were divided into normal, diastolic dysfunction and systolic dysfunction. In the 25 patients with a normal LV function, BNP levels averaged 14±4 pg/mL, and were lower than in those with abnormal cardiac function (71.8±13.3 pg/ml $p<0.0001$), in abnormal group, BNP levels were lower in those with either diastolic dysfunction (n=29, BNP=68±14 pg/mL, $P<0.0001$) or systolic dysfunction (n=9, BNP=224±41 pg/mL, $P<0.0001$). Well-controlled patients (n = 18) receiving cardiac drugs had abnormal diastolic LV function but similar BNP levels to those of patients with normal LV function (BNP=21±7 vs. 14±4 pg/mL, P=0.34). ROC analysis revealed an AUC of 0.88 for the detection of LV diastolic or systolic dysfunction and an AUC of 0.91 for the detection of systolic dysfunction. The best cut-off of BNP levels to detect LV dysfunction was 33 pg/mL (accuracy=80%, sensitivity of 84%, specificity of 76% positive and negative predictive values (PPV, NPV) of 88% and 69%, respectively). For the detection of LV systolic dysfunction, the best cut-off was 120 pg/mL (accuracy=82%, sensitivity of 83%, specificity of 78% and PPV=78% and NPV=83%, respectively). Age, LV mass index, LVEDD and LVESD were significantly and independently correlated with BNP (multivariate r=0.80, P=0.0002, 0.03, 0.002 and 0.01, respectively).
Conclusions: In asymptomatic diabetic patients, BNP levels could accurately predict LV dysfunction and may be helpful for monitoring therapy. A level <33 pg/mL may preclude the need for expensive echocardiography.

P2961 NT-pro Brain natriuretic peptide as marker for severity and prognosis of left ventricular dysfunction

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Brain natriuretic peptide (BNP) is secreted from the ventricles upon stretch, and BNP plasma levels are elevated in congestive heart failure. We determined the value of plasma levels of NT-pro BNP, the inactive N-terminal cleavage product during activation of BNP, for diagnosis of inapperent left ventricular dysfunction and assessement of prognosis in patients with overt heart failure.

Methods: Clinical evaluation of 30 healthy controls, 196 asymptomatic patients with cardiovascular risk profile (hypertension, diabetes, hyperlipidemia), but no known ventricular dysfunction (risk patients, RP), and 98 patients with echocardiographically demonstrated reduced left ventricular function (EF <40%; LV-Dys). Correlation of clinical parameters with NT-proBNP plasma levels (Elecsys, Roche Diagnostics, Tutzing, Germany).

Results: NTproBNP plasma levels were 36±4 pg/ml in controls, 251±62 pg/ml in RP ($p<0.01$ vs. controls), and 4716±695 pg/ml in LV-Dys ($p<0.001$ vs controls or RP). In RP, NT-proBNP plasma levels were positively correlated with systolic hypertension ($p<001$), pathological echocardiographic findings (LV hypertrophy, pathological E/A ratio, EF, LVEDD; p=0.037) and proANP plasma levels ($p<0.01$). In LV-Dys, NT-proBNP levels increased significantly with increasing NYHA class (NYHA I: 1759±855; NYHA II: 3027±605; NYHA III: 4271±733; NYHA IV: 10816±2623 pg/ml). There was a direct correlation between NT-proBNP levels and NYHA class (r=0.544; $p<0.001$), EF (r=-0.234; p=0.034), or age (r=0.249; p=0.041). In patients with normal kreatinine values (n=44), the correlation with NYHA class (r=0.621; $p<0.001$) or EF (r=0.417; p=0.006) was even better. After 1 year, 20 of 109 patients in LV-Dys (18.3%) had died. In these patients, the initial NT-proBNP levels (29.004 pg/ml) were significantly ($p<0.001$) higher than in survivors

P2962 Value of cardiopulmonary exercise testing and brain natriuretic peptide to predict prognosis of patients with chronic heart failure

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Background: Cardiopulmonary exercise testing (CPX) and determination of brain natriuretic peptide (BNP) are used to estimate survival in patients (pts) with chronic heart failure (CHF). No data, however, exists comparing the prognostic value of both methods in a cohort of pts with moderate to severe CHF simultaneously.

Methods: We prospectively studied 85 consecutive CHF pts (59 ± 13 y., 63 men, LVEF 26 ± 6%, NYHA II-III, 34 ischemic heart disease, 51 dilated cardiomyopathy) with regard to the incidence of cardiac decompensation and/or cardiovascular mortality. At study entry all pts underwent a symptom-limited CPX with determination of peak VO2 and resting BNP plasma level.

Results: During the study period of 273 ± 142 days, 2 pts (2.4%) were lost to follow-up, 4 pts (4.8%) died from cardiac disease, and 10 pts (12.2%) suffered from cardiac decompensation. Kaplan-Meier estimates of freedom from cardiac decompensation/death differed significantly both for pts above and below the median values of BNP and peak VO2. The event-free survival rate was 95% in pts with a plasma BNP < 292 pg/ml (median value) compared to only 76% in pts with a BNP > 292 pg/ml ($p < 0.05$). CPX resulted in comparable findings with an event-free survival rate of 95% in pts with a peak VO2 > 15.3 ml/min/kg (median value) compared to only 76% *in* pts with a peak VO2 < 15.3 ml/min/kg ($p < 0.05$).

Conclusions: Plasma BNP seems to be a valuable tool for risk stratification in pts with moderate to severe CHF. BNP was comparable to the prognostic power of peak VO2. Thus BNP might help to reduce the need for more expensive and time consuming cardiac tests like CPX in the management of CHF.

P2963 Determination of a prognostic threshold for bedside B type natriuretic peptide in chronic heart failure

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NYHA classification and left ventricular ejection fraction are the major prognostic factors used in routine in chronic heart failure. BNP is a peptide secreted by the myocytes. We thus wanted to determine the interest of measuring bedside BNP compared to the traditional prognostic factors

Methods BNP plasmatic level was determined by bedside ultra fast "triage" immuno-fluorescent assay (Biosite laboratories). Left ventricular ejection fraction was determined by echocardiography.

Results We included 171 consecutive patients. The follow-up was 6 months. The patients were separate in two groups at the end of the follow-up. Group A included patients alive and the group B the patients deceased of heart failure during the follow-up. The group B presented a higher NYHA class (respectively 3,75±0,44 versus 2,28±1,05 $p<0,001$), a lower LVEF (28,5%±8,21 versus 37,7±8,8 $p< 0,001$) and a much higher BNP level (1208±166 versus 295±54,3 pg/ml $p< 0,001$) than group A. In univaried analysis, LVEF and BNP level can predict mortality (respectively $p< 0,04$ and $p<0,001$). In multivariate analysis, only BNP level is an independent prognostic factor ($p<0,001$).

Mortality is null in the group of the patients presenting a left ventricular ejection fraction < 35% having normal BNP and is about 47% at the end of the follow-up in the group of the patients with a left ventricular ejection fraction < 35% and a BNP > 300 pg/ml Mortality is related to the BNP level more than to the LVEF and NYHA class. In ROC curves, 800 pg/ml of BNP seems to be the best threshold to predict mortality at 6 month.

Conclusions the plasmatic BNP level obtained in routine is a very good prognostic marker in chronic heart failure. Patients with a BNP < 300 pg/ml have a good prognosis regardless to LVEF or NYHA classification. It allows to determine the prognosis of patients suffering from chronic heart failure in a finer way than the LVEF or NYHA class.

P2964 N-terminal brain natriuretic peptide (N-BNP) and atrial natriuretic peptide (N-ANP) in healthy neonates: marked and rapid increase after birth

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The purpose of the study was to examine possible variances in the expression of N-BNP and N-ANP during the developmental circulatory changes after birth in healthy term neonates. Reference values for N-BNP and N-ANP in neonates are not known.

Methods: N-BNP and N-NP plasma concentrations were measured in peripheral venous (n=116) and umbilical cord blood (n=37) in 153 healthy term neonates (5.1,0 – 30 days) using a validated enzyme immunoassay. For comparison the newborns were divided into eight different age groups from birth to 30 days of age.

Results: The plasma N-BNP and N-ANP concentrations were the highest at 1 day of age (600, 254-893 and 110350; 10000 - 436000 fmol/ml) and were found significantly higher compared to 0 days of age (201, 58-430 and 5680 - 16900; $p<0.0001$). After this marked increase N-BNP and N-ANP levels decrease regularly and become stable at the fifth day of life.

Conclusion: The N-BNP and N-ANP plasma concentrations in healthy neonates showed a marked and preferential increase during the first days of age, suggesting that these natriuretic peptides have a physiological role in the perinatal change from fetal to neonatal circulation.

EXERCISE TRAINING IN HEART FAILURE

P2965 Assessment of ventilatory response to exercise in patients with chronic heart failure

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In chronic heart failure (CHF), cardiopulmonary exercise testing (CPX) is useful in monitoring clinical severity of the disease, determining the optimal timing of heart transplantation and for risk stratification. The aim of this study was to assess the practical value of newly described parameter derived from CPX i.e. the ventilatory response to exercise in unselected population of CHF pts.

Material and methods: We investigated 80 consecutive, stable CHF pts (61 men, age: 61 yrs, NYHA class I/II/III: 9/39/32, left ventricular ejection fraction [LVEF]: 33%) and 20 age- and sex-matched healthy controls that underwent CPX. The regression slope of minute ventilation against carbon dioxide production (VE/VCO2 slope) was used as an index of ventilatory response to exercise. In addition, peak oxygen uptake (peak VO2) and anaerobic threshold (AT) were measured.

Results: When compared to the control group CHF patients had lower peak VO2 (17.9±4.1 vs 32.4±7.1 ml/kg/min) and higher VE/VCO2 slope (34.8±10.1 vs 23.9±4.1, CHF vs controls respectively, $p<0.001$ for both comparisons). VE/VCO2 correlated neither with age nor with indices of left ventricular function (ejection fraction, diastolic and systolic diameters)($r<0.2$, $p>0.1$ in all analyses). However, we found correlation between VE/VCO2 and peak VO2 ($r=-0.51$, $p<0.001$), NYHA class (NYHA I-II vs III, $p<0.001$) and quality of live as assessed by the Minnesota questionnaire ($r=0.39$, $p<0.05$). To investigate reproducibility of VE/VCO2 slope 14 CHF pts and 10 controls underwent a second CPX within 10-18 days. In both groups VE/VCO2 slope had acceptable reproducibility (coefficient of variance of 14% in CHF and 11% in controls). During the follow-up (average 11 months) 10 (13%) CHF pts died. Augmented VE/VCO2 was related to poor prognosis independently of peak VO2, NYHA class and impaired left ventricular function ($p<0.05$).

Conclusions: In a broad, unselected population of CHF patients, increased exercise ventilation (VE/VCO2 slope) correlates with the objective and subjective indices of exercise intolerance, and may per se have a prognostic value. The assessment of VE/VCO2 could be used as an additional, simple and reproducible CPX-derived parameter in patients with CHF.

P2966 Improvement of regional myocardial function following exercise training in left ventricular dysfunction measured by Doppler myocardial imaging

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The aim of the study was a quantitative assessment of the effects of exercise training on regional systolic and diastolic myocardial function in patients (pts) with left ventricular (LV) dysfunction, using pulsed wave Doppler myocardial imaging (PW-DMI).

Method: In the group of 51 male pts (mean age 56.7 ± 8.7 years) with ejection fraction (EF) < 40%, at baseline and after four weeks echocardiography studies were performed.

Regional myocardial function, was obtained from apical approach, with PW-DMI sample volume within any LV segment at basal and medium level. In each adequately visualized segment we calculated m.v. of systolic (S), early (E) and late (A) diastolic waves and their ratio E/A - index of regional diastolic function. After the initial study, pts were randomized to trained (T, n=32) and control (C, n=19) groups. Patients in T group exercise daily about 40 minutes in the 10 to 15 minutes intervals over a period of four weeks at a residential rehabilitation center while pts in C group received usual community care.

Results: After four weeks, in the T group regional diastolic function of basal and medium LV segment significantly improved (E/A from 0.88 ± 0.39 to 0.98 ± 0.41, $P<0.05$ and E/A from 0.82 ± 0.37 to 0.95 ± 0.42, $P<0.01$) as well as regional systolic function (S from 7.2 ± 3.1 to 8.0 ± 3.3 cm/s, $P<0.05$ and S from 6.7 ± 3.3 to 7.5 ± 3.5 cm/s, $P<0.05$). In the C group evaluation of regional diastolic function of basal and medium LV segments showed slightly changes (E/A from 0.89 ± 0.36 to 0.93 ± 0.39, NS and E/A from 0.86 ± 0.35 to 0.89 ± 0.38, NS) as well as regional systolic function (S from 6.8 ± 3.1 to 7.1 ± 3.5 cm/s, NS and S from 6.0 ± 2.9 to 6.4 ± 3.3 cm/s, NS). EF increased slightly in the T group but was not changed in the C group.

Conclusion: In LV dysfunction exercise training significantly improved regional systolic and diastolic myocardial function which can be estimated by PW-DMI, even before significant changes in LV EF occurred.

P2967 Exercise training decreases biventricular oxidative metabolism and improves left ventricular efficiency in patients with dilated cardiomyopathy

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The effect of exercise training on myocardial oxidative metabolism and efficiency was studied in 16 clinically stable patients with dilated cardiomyopathy (NYHA class I-II) using positron emission tomography (PET) techniques. Nine of these patients participated in a 5 month endurance and strength training program at an intensity of 70% of peak oxygen consumption (VO2), while 7 patients served as control subjects. Measurements of left ventricular function were assessed using two-dimensional echocardiography. Basal oxidative metabolism in both the left (LV) and right (RV) ventricle were measured using the monoexponential clearance rate of [11C]acetate (kmono). An estimation of myocardial work per gram of tissue was calculated as (systolic blood pressure x stroke volume x heart rate)/LV mass. Myocardial efficiency was calculated as myocardial work/LVkmono. The patient groups were comparable at baseline in terms of LVkmono, LV work, and LV efficiency, however baseline RVkmono values were slightly lower in the training group compared to the control group. Peak VO2 increased by 27% in the training group (19.4±4.1 to 24.6±5.2 ml/kg/min; $P<0.001$) where no change was observed in the control group (20.6±4.2 to 21.2±2.9 ml/kg/min; P=NS). An improvement in ejection fraction was also observed in the training group (33±8 to 39±9%; P=0.004) compared to the control group (35±7 to 37±6%; P=NS). Biventricular oxidative metabolism along with LV work and efficiency results are shown in the table.

	Training group		Control group	
	Baseline	Follow-up	Baseline	Follow-up
RVkmono (/min)	0.047±0.006#	0.0421±0.007*	0.056±0.006#	0.0570±0.009
LVkmono (/min)	0.065±0.014	0.059±0.016*	0.073±0.012	0.074±0.014
LV work (mmHgxml/g)	1.88±0.74	2.02±0.63	2.46±0.55	2.54±0.59
LV efficiency (mmHgxml/g/min)	28.8±9.8	34.4±7.9*	33.6±6.9	34.2±5.4

*P<0.05 (Baseline vs. Follow-up); #P<0.05 (between groups).

Exercise training improved LV function and exercise tolerance while biventricular oxidative metabolism decreased. This decrease resulted in an enhanced LV efficiency. Therefore, we conclude that exercise training is an energetically favorable way to improve myocardial function and exercise tolerance in patients with dilated cardiomyopathy and mild heart failure.

P2968 Augmented plasma adenosine response to exercise and reduced exercise ammonia in heart failure: a possible alteration of purine degradation

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Background: During strenuous muscle exercise, purine nucleotide degradation occurs and adenosine monophosphate (AMP) is metabolized into two pathways. One is deamination by AMP deaminase, an enzyme responsible for ammonia production, and other is dephosphorylation by 5'-nucleotidase, an enzyme responsible for adenosine production. Recently, it has been reported that inheritance of the mutant AMP deaminase 1 allele is associated with good prognosis in patients with chronic heart failure (CHF). Such patients have reduced AMP deaminase activity in their skeletal muscle and might have enhanced adenosine production with relative activation of 5'-nucleotidase. This study determined whether plasma adenosine response to exercise is augmented in patients with CHF.
Methods: Maximal ergometer exercise tests with expired gas analysis were performed in 51 patients with CHF (age=61±2 years, left ventricular ejection fraction=38±1%, peak VO2=18.0±0.7 ml/min/kg, NYHA class I/II/III=19/18/14) and 20 normal controls. Serial changes in plasma ammonia and adenosine were determined. The exercise response was assessed by the ratio for the change (delta) in each metabolite to peak work rate.
Results: Peak work rate decreased as CHF worsened (Control, NYHA I, II, III: 155±11, 141±10, 97±8, 72±7 watts, $p<0.0001$). Resting plasma adenosine, but not ammonia, were higher in class III CHF (22±5, 17±4, 31±7, 46±13 nmol/L, $p<0.05$). The changes in plasma ammonia by exercise were smaller as CHF worsened. The ratio for delta-ammonia to peak work rate was smaller in class III CHF (0.59±0.13, 0.41±0.06, 0.37±0.10, 0.22±0.11 μg/dL.watts, $p<0.05$). Plasma adenosine response to exercise tended to be augmented in class III CHF, and the ratio for delta-adenosine to peak work rate was significantly augmented in class III CHF (0.90±0.20, 0.86±0.14, 1.11±0.27, 2.92±0.67 nmol/L.watts, $p<0.001$).
Conclusions: Plasma adenosine levels were significantly higher, and adenosine response to exercise normalized with the peak work rate was augmented in patients with severe heart failure. On the other hand, plasma ammonia response was attenuated. These results suggest that there may be an altered adenine nucleotide metabolism with shunting of ATP catabolic pathway from AMP deamination to adenosine production. Given the physiological actions, the enhanced adenosine production at rest and during exercise may have cardioprotective effects in patients with CHF.

P2969 Combination of submaximal and maximal exercise testing for improvement of prognostic assessment in heart failure

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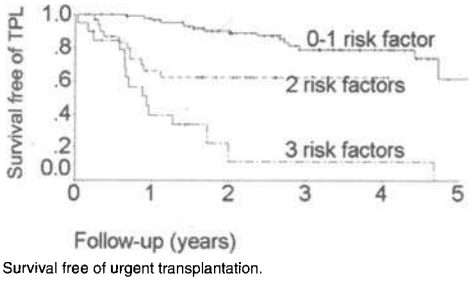
Peak exercise testing has been used for long to assess prognosis in congestive heart failure (CHF). More recently, there has been an increasing interest in submaximal exercise testing, trying to substitute maximal exercise testing. However, maximal and submaximal exercise testing may not test the same. Thus, combining the 2 tests may augment the predictive value of exercise testing.
Methods: Ergospirometry was performed in 146 patients with CHF (EF 27±13%), using a 2-step treadmill protocol (first 6 minutes 1mph, 6% elevation, followed by a ramp protocol 0.15W/kg/min). The mean response time (MRT=O2-deficit/DVO2) of VO2 during initiation of exercise and peak oxygen consumption (VO2max) were measured. DVO2=difference of VO2 from rest to steady state. Cardiac death and urgent transplantation were considered as endpoints (follow-up 27±17months).
Results: Thirty-two patients (22%) died and 11 (8%) were urgently transplanted. In multivariate Cox-regression analysis, MRT (hazard ratio (HR) for combined endpoint: 1.68 per 10s, $p<0.0001$), VO2max expressed as % of normal value (HR=0.62 per 10%, $p<0.0001$), and resting systolic blood pressure (SBP; HR=0.71 per 10mmHg, $p=0.003$) were independently related to prognosis. The following cut-off points were used (combined endpoint, all $p<0.001$): MRT>50s (HR=4.47), VO2max<50% (HR=4.67), resting SBP<105mmHg (HR=3.11). Patients with all 3 risk factors (n=20) had a very bad prognosis (mortality/combined endpoint: 1 year: 49%/60%; 2 years: 83%/89%), while patients with no or only one factor (n=94) were not at particular risk (1 year: 3%/3%; 2 years: 10%/11%; figure).
Conclusion: The combined use of parameters of submaximal and maximal exercise testing provides a more complete picture for risk assessment in CHF.



Survival free of urgent transplantation.

P2970 VE/VCO_2 slope normalized for the achieved exercise workload (Watts) better predicts prognosis than the VE/VCO_2 slope in heart failure

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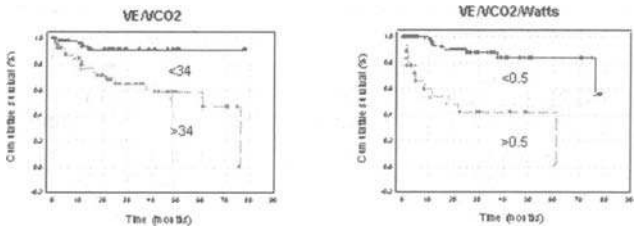
Background: The level of physical activity is tightly related to prognosis in chronic heart failure (CHF). The slope of the VE/VCO2 relationship during exercise is a strong predictor of survival in CHF. Nevertheless, this parameter does not account for endurance and intensity of exercise.
Aim of the present study was to assess whether normalization for the achieved exercise workload (Watts) strengthens the prognostic power of the VE/VCO2 slope in CHF.
Methods: For this purpose, we enrolled in a prospective study 100 patients (78 men, 22 women), mean age 60±9 years, NYHA class II-III, with mean ejection fraction of 35±10% in stable haemodynamic conditions and optimized pharmachological therapy. Patients underwent maximal cardiopulmonary testing by cycloergometer (personalized ramp test).
Results: The mean value of oxygen consumption at peak exercise (peak VO2) was 16.2±4.3 ml/kg/min and the averages of VE/VCO2 slope and VE/VCO2/W were 34±8 and 0.39±0.2, respectively. The mean follow-up of the study was 26.5±2 months.
The survival curves analysis by Cox regression hazard method showed that long term prognosis is better predicted by the VE/VCO2/W, than the VE/VCO2 ($p<0.0001$ vs $p<0.03$). Figures show Kaplan Meier curves for VE/VCO2 slope (cut-off: 34) and VE/VCO2/W ratio (cut-off: 0.5).



Kaplan Meier survival curves.

Conclusions: These results document that both VE/VCO2 and VE/VCO2/W are related with mortality. Nevertheless, normalization of VE/VCO2 slope for the achieved exercise workload strengthens the prognostic power of this relevant clinical indicator.

P2971 Lower prognostic value of peak VO_2 compared with the exercise ventilatory response in the patients with heart failure on beta-blocker therapy

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Long-term beta-blocker (BB) administration to the patients with chronic heart failure (HF) is associated with a significant improvement in left ventricular ejection fraction (LVEF) and hemodynamics with only small changes in maximal functional capacity. We thus hypothesised that the prognostic value of these parameters could be influenced by BB therapy. One-hundred eighty-four patients with HF (LVEF, 20±7%; peak VO2, 14.3±4.5 ml/k/min) were assessed by MUGA and cardiopulmonary exercise (ex) testing with invasive hemodynamic monitoring before and, in the 164 patients (89%) who survived, after 9-12 months of maintenance therapy with carvedilol (n=102; 41±17 mg/day) or metoprolol tartrate (n=62; 106±45 mg/day). During the 29±20 months of follow-up after the reassessment on BB therapy, 28 of the 164 patients (18%) died and 16 underwent heart transplantation (Tx). Among the parameters assessed before the initiation of BB therapy, Cox multivariate regression analysis selected peak VO2 (HR, 0.83; 95%CI, 0.75-0.91; p=0.0002) and serum creatinine (p=0.002) as significant predictors of total mortality and, similarly, serum creatinine (p=0.007), peak VO2 (p=0.002) and NYHA class (p=0.004) as predictors of mortality and Tx. In contrast, when the data obtained during BB therapy were used, the variables selected were serum creatinine (p=0.005), VE/VCO2 slope (HR, 1.06; 95%CI, 1.01-1.10, p=0.009), age (p=0.027) and resting PWP (p=0.035). Six, 12, 24 and 36 months cumulative survival was of 97%, 96%, 94% and 94% respectively, in the patients with peak VO2 > 14 ml/kg/min, 98%, 90% and 83% and 77% in the patients with peak VO2 < 14 and > 10 ml/kg/min and 74%, 64%, 59% and 51% in the patients with peak VO2 < 10 ml/kg/min (p<0.001 at log-rank tests). Six, 12, 24 and 36 months survival was 98%, 96%, 92% and 88% in the 65 patients with a normal, <35, VE/VCO2 slope and 91%, 83%, 79% and 76% in the other 99 patients with a VE/VCO2 slope > 35 (p<0.001). Peak VO2 was highly related to peak ex heart rate (HR), CI, stroke volume index (SVI), mean pulmonary artery pressure (PAP) and PWP (r= 0.44, 0.77, 0.61, -0.37 and -0.34, respectively; all p<0.001) while VE/VCO2 slope was less related to peak ex HR (r=-0.15), CI (r=-0.53) and SVI (r=-0.51). Thus, maximal functional capacity remains useful for the prognostic assessment of the HF patients on BB therapy. The lower prognostic value of peak VO2 may be related to its greater dependence on the HR and CI response to ex which may be influenced by BB therapy independent from its beneficial effects on LV function.

P2972 Effect of exercise training on skeletal muscle metabolism in patients with dilated cardiomyopathy

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Most training studies related to chronic heart failure involve a combination of patients with an etiology of ischemic and idiopathic cardiomyopathy. Due to limited data available regarding on effect of exercise training on skeletal muscle metabolism in patients with idiopathic dilated cardiomyopathy (DCM) we aimed to determine the adaptive peripheral changes in perfusion and metabolism in DCM after combined aerobic and resistance training.

Fifteen, NYHA I-II, DCM patients on stable medical therapy were studied. The subjects were prospectly selected to either a training group (n=8, LVEF=34±8%) or a non-training group (n=7, LVEF=36±6%) based on residence. The training program lasted for five months, 3 days/week at an intenisty of 65-70% of VO2max. Also, 2 days/week home training was included into program. Training consisted of both strength and endurance training components. Muscle blood flow, oxygen consumption, and glucose uptake was quantified using [15O]-water, [15O]-oxygen, [18F]-FDG, and positron emission tomography (PET). Subjects performed one-legged isometric exercise at an intensity of 10% of maximal isometric force during scanning. The measurements were done during euglycemic hyperinsulinemic clamp before and after exercise training or equal control period.

Attendance in the training program was 88%. Average improvement in exercise capacity was 27% in training group, p<0.001. Training improved whole body glucose uptake (23%, p<0.05), resting (53%, p=0.08) and exercise stimulated glucose uptake (55%, p<0.05). Changes in resting or exercise stimulated blood flow or oxygen uptake were not observed after training. Measured variables remained unchanged in control group.

Training was safe and it improved exercise capacity efficiently in this patient group. Insulin sensitivity was improved along with insulin and exercise stimulated skeletal muscle glucose uptake by training. Therefore, regular exercise with combined strength and endurance training was beneficial for these patients and counteracts the metabolic disturbaces caused by DCM.

DIAGNOSIS AND MONITORING OF HEART FAILURE

P2973 Elevation of biochemical markers of myocardial injury associated with pulmonary embolism

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The introduction of cardiac specific troponin estimation has improved the recognition and management of patients with acute coronary syndromes (ACS). However, conditions other than ACS may also present as emergencies with acute chest pain and dyspnoea, such as acute pulmonary embolism (PE). The tendency to assume that elevation of these biochemical markers always indicates coronary artery disease may potentially result in incorrect diagnosis and inappropriate investigation. We present results from an epidemiology study into the investigation and management of confirmed pulmonary embolism in Southampton, UK (population 430,408).

Over a one-year period in Southampton University Trust Hospitals 219 cases of pulmonary embolism were confirmed by ventilation perfusion lung scan or helical computerised tomographic pulmonary angiography. Due to diagnostic uncertainty at presentation, biochemical markers of myocardial injury (creatinine kinase [CK] and troponin) were requested by clinicians in 71 cases (38 had creatinine kinase levels only, 10 troponin had levels only, and 23 had both CK and troponin measured). 3 patients had troponin levels >1.5ug/L, 2 of whom also had CK levels >250IU/L. 8 further patients had troponin levels between 0.15 -1.5ug/L without CK elevation, 5 patients had an elevation of CK >250IU/l without troponin measurement and 4 patients had troponin levels 0.15 -1.5ug/L without CK measurement. Thus, 20 of 71 (28.1%)of patients with confirmed PE had elevation of either CK or troponin levels.

An elevated troponin or CK may be found in acute pulmonary embolism and therefore the detection of a raised biochemical marker of myocardial injury does not necessarily indicate ACS or exclude a clinically suspected acute PE. The mechanisms by which these markers are raised in acute PE may be multifactorial but will include myocardial ischaemia induced by acute right heart strain or haemodynamic compromise due to massive PE. Further research is required to determine whether elevation of these markers is related to prognosis or if they may be used to indicate potential benefit from thrombolysis therapy in acute PE.

P2974 Coronary angiography in CHF patients with no history of ischaemic heart disease. A clinical study

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The aim of the present study was to verify the clinical usefulness of coronary angiography (CA) in a consecutive series of CHF patients admitted to our heart failure clinic. Indication to CA was proposed following the recent European guidelines in order to elucidate the cause of CHF and to assess prognosis. Among 112 patients with history of heart failure and LVEF < 40% who underwent CA, 51 subjects (mean age 63±10 yrs, LVEF 32±6%, NYHA cl. II-III) were studied for uncertain aetiology of the disease. When not contraindicated an effort test or Echo-dobutamine test were performed before CA in all these patients. Diabetes, hypertension and dislipidemia were present respectively in 20%, 41% and 20% of the 51 patients, while none suffered of previous myocardial infarction or angina.

After non invasive procedures an ischemic aetiology was suggested in 6 patients, all affected by diabetes plus an other risk factor. CA showed normal coronary arteries in 42, one vessel in 4, two vessels in 4 and three vessels in 1 subject. Four out of 5 patients with two or three vessels disease were treated with PTCA or CABG. In the absence of diabetes and a positive non-invasive test, CA showed normal coronary arteries in 100% of the patients.

Conclusion: In those CHF patients who: i) do not present positive history of ischemic heart disease, ii) have no angina or diabetes, iii) can be submitted to a valid functional test which results negative, coronary angiography does no give further clinical information and may be avoided. This approach will allow to significantly reduce the high costs of treatment of heart failure with undetermined aetiology.

P2975 Circadian distribution of onset of acute pulmonary oedema in 206 consecutive patients with or without coronary artery disease

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In 206 consecutive patients admitted within 12 hours of onset of an acute cardiogenic pulmonary edema (APE) the clinical and echocardiographic characteristics were prospectively investigated, with especial emphasis in the time of onset of respiratory symptoms. Patients with chronic heart failure or those with progressive heart failure over a period of >12 hours were excluded. In 176 (85%) a diagnosis of coronary artery disease (CAD) was based on a history of myocardial infarction, presence of angina with ECG changes during APE, coronary estenosis >70% in =>1 main vessel or clear scintigraphic evidence of reversible ischemia. Of the remaining 30 patients,10 presented isolated valvular heart disease (5%), 10 hypertensive cardiomyopathy (5%) and 11 had other cardiac disease (5%).

The mean interval between onset of APE and hospital admission was 3.3±2.7 hours. Circadian presentation was distributed in 3 intervals of 8 hours: 05-12 (a), 13-20 (b) and 21-04 (c). Overall, 109 (53%) patients presented APE in c, 58 (28%) in a and 39 (19%) in b ($p<0.001$). Patients with CAD showed a similar distribution: 91 (50%) in c, 51 (28%) in a, and 33 (18%) in b ($p<0.001$) than those without CAD: 16 (55%) in c, 7 (24%) in a and 6 (21%) in b ($p<0.05$). Moreover, among patients with rapid atrial fibrillation (>130 beats/min) as trigger of APE (n:29), 21 with CAD and 8 without, the circadian distribution (c: 16 (53%), a: 5 (17%) and b 8(27%)($p<0.04$)) was also similar (p: ns) than in those without rapid atrial fibrillation (c:93 (53%), a:53 (30%), and b 31 (17%)($p<0.001$)).

Conclusion: In >50% of patients with APE onset of sypmtoms occurs from 21-04 hours and in only <20% it occurs from 13-20 hours. This nocturnal predominance appears to be independent of the underlying kind of heart disease or trigger of this event.

P2976 Myocardial damage detected by troponin T in heart failure is associated with low functional capacity in the 6-minute walk test

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Background: Six minute walk test offers an objective measures of functional capacity (FC) and yields prognostic information in patients (pts) with chronic heart failure (CHF). Ongoing myofibrilar degradation has been detected by troponin T (cTnT) in CHF. We hypothesize that myocardial damage could be associated with a low FC in pts with CHF.

Methods: Between 01/2001 and 03/2001, 153 outpatients from a Heart Failure Program were prospectively included. Patient's evaluation included clinical examination, ECG, echocardiography and biochemical test. Baseline cTnT of 3° generation >=0.02 ng/mL was considered abnormal. Low functional capacity was defined as a walked distance <300 mts and was present in 33 pts (21.5%)(Group 1).

Results: Mean age of group 1 was 70±9 vs. 60±11 years in pts without low FC (Group 2)($p<0.001$), and women were 54.5% vs. 27%, respectively ($p=0.002$). Intermittent claudication was more frequent in group 1(18 vs. 5%, $p=0.01$) and NYHA functional class was higher (2.81±0.5 vs 2.14±0.9). Ischemic etiology was similar between groups, but hypertensive etiology was more prevalent in group 1 (36 vs 16%, $p=0.009$). cTnT >=0.02 ng/mL was detected in 45% of group 1 and 20% of group 2 ($p=0.003$). In a multiple regression analysis, independent variables associated with a low FC were: age (OR=1.09, CI=1.03-1.16, $p=0.002$), functional class (OR=2.9, IC=1.3-6.4, $p=0.009$), female gender (OR=4.7, IC=1.7-13.3, $p=0.003$), hepatomegaly (OR=10.9, IC=1.1-103, $p=0.03$) and myocardial damage (OR=3.3, IC=1.2-9.4, $p= 0.02$).

Conclusion: Low FC in a walk test was present in a quarter of patients with CHF and it was associated with clinical characteristics such as age, female gender and NYHA class as well as increased level of cTnT. The biochemical evidence of ongoing myocardial injury in CHF stable patient was a strong predictor of low performance in 6-minute walk test.

P2977 Endocardial acceleration based implantable system for monitoring acute ventricular failure

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Acute volume overloading leading to acute heart failure and possibly to death is not a rare event in clinical practice and no implantable systems able to alert such dramatic events are currently available. Peak endocardial acceleration during isovolumic contraction phase (PEA I) is determined by left ventricle (LV) dP/dtmax changes and during isovolumic relaxation (PEA II) by both aortic pressure and LVdP/dtmin.

Aims of this study: 1) to test the capability of an implantable endocardial acceleration (EA) sensor to immediately detect systolic and diastolic impairment during LV acute volume overload, as documented by LV end diastolic pressure (LVEDP).

Methods: in 6 anesthetized sheep (63 ± 4Kg) an EA sensor, housed in the tip of a standard pacing lead (Best, Sorin), was screwed in the apex of the right ventricle. A Millar catheter was positioned in the LV to monitor LVdP/dtmax, LVdP/dtmin and LVEDP; external ECG was recorded. Once basal data were acquired 2L liters of glucose solution (10%) were acutely infused through the jugular vein in 10 min.

Results: at 1L volume overload PEAI suddenly increased from 0.57±0.24 g to 0.93±0.40g, strictly related to LVdP/dtmax variation from 798±373 mmHg/s to 1021±280 mmHg/s at 1L and to LVEDP increase from 12.7±0.5 mmHg to 21.2±4.5 mmHg.

After an initial phase of increase of PEAII (from 0.22±0.10 to 0.28±0.09 g), extremely sensitive to LVEDP increase, a drop of both PEA II and LVdP/dtmin occurred at 2L volume overload, when LVEDP reached values (31±4mmHg) indicative of LV dilation and lung edema.

Conclusions: The EA sensor was able to detect 1L acute volume when acute recruitment of LV function through the Starling mechanism occurred. A PEA I and PEA II based survey system for hemodynamically instable pts can promptly alert life threatening events of acute volume overload and acute diastolic failure. This implantable EA based system opens a new window in early and effective alert systems for patients that risk acute volume overloading.

P2978 Clinical and etiological features, management and outcomes of acute heart failure: the EFICA cohort study

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Introduction: Acute heart failure (AHF) accounts for 14,000 hospitalisations per year in France which is twice as many as hospitalisation for acute MI. Yet, no recent observational study of AHF is available for reference. Furthermore, compared to chronic HF, AHF has been the subject of very few clinical trials.

Methods: EFICA (Etude d'observation Francaise de l'Insuffisance Cardiaque Aiguë) is an observational cohort study with prospective case ascertainment of patients admitted consecutively from May to December 2001 to 60 representative CCUs and ICUs in France, with the diagnosis of AHF.

Results: A total of 599 patients were enrolled. They were aged 73 [25-98], and had the following characteristics: aged above 80: 31%; male 58%; admitted through an emergency unit: 54%; previously diagnosed with CHF: 65%; previously admitted for AHF: 35%. AHF most frequent causes were ischemic heart disease 60%, dilated cardiomyopathy 28%, valvular disease 25% and hypertension 21%. The most frequent precipitating factors were acute myocardial ischemia 36%, arrhythmia 26%, infection 18%. On admission 82% had pulmonary oedema and 29% had cardiogenic shock. Echocardiography was performed on admission in 400 pts. Median LVEF (measured in 322 pts) was 35%. LVEF was >45% in 26% of pts. On admission 52% of pts were receiving diuretics, 42% ACE inhibitors and 23% betablockers. CKMB was measured in 240 pts among which 37% had abnormal levels. Troponine I, measured in 337 pts was high in 46%. Serum creatinine was elevated in 51%. During hospitalisation, 60% received ventilatory assistance, 4% circulatory assistance 53% inotropic support (82% dobutamine) and 3 pts heart transplant. Median length of stay (LOS) at ICU was 4 days [1-79] and total LOS was 12 days[1-113]. In-hospital mortality was 29% among which 76% was related to cardiogenic shock, 25% acute MI and 12% ventricular arrhythmia deaths. Sudden death accounted for 18% of total deaths.. Six month outcome data and prognostic analyses are currently being performed and will be presented at the meeting.

Conclusion: EFICA provides an up-to-date database on clinical and etiological features, management and outcomes of AHF which are critical for designing new management strategies and clinical trials specific to this deadly condition.

PULMONARY CIRCULATION

P2979 NT-pro brain natriuretic peptide as novel marker for diagnosis and prognosis of acute pulmonary embolism

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Plasma levels of brain natriuretic peptide (BNP) are increased in heart failure, but no data are available for changes in BNP levels during acute pulmonary embolism. We tested plasma levels of NT-proBNP (pBNP), the N-terminal cleavage product during activation of BNP, in patients admitted with acute pulmonary embolism (PE).
Methods: 31 patients with acute PE; diagnosis by clinical signs + echocardiography + spiral CT or ventilation/perfusion scintigraphy. Determination of NT-proBNP plasma levels (Elecsys, Roche Diagnostics) upon admittance and after 4,8, and 12 hours.
Results: pBNP was massively elevated in PE upon admittance, as compared to control persons (5118±1985 vs. 36±4 pg/ml, $p<0.05$). pBNP levels further increased to 5669, 5934, and 6352 pg/ml after 4,8, and 12 hours, respectively. In patients with right ventricular dilatation (RV-dil) on echocardiography (n=6), pBNP was significantly higher as compared to patients without RV-dil (20059 vs. 1706 pg/ml, $p<0.05$). We observed a close correlation between RVEDD (in mm) and pBNP levels ($r=0.651$; $p<0.001$). In patients with RV-dil, pBNP markedly increased during the first 12 hours (to maximally 29941 pg/ml after 4 hours; $p<0.001$), but did not change in patients without RV-dil. Patients with clinical complications (iv catecholamines, intubation, resuscitation or death; n=7) had significantly higher pBNP levels upon admittance as compared to patients with uncomplicated clinical course (32428 vs. 1706 pg/ml, $p<0.001$).
Conclusion: NT-proBNP plasma levels markedly increase during acute pulmonary embolism. This increase correlates with RV dilatation and clinical complications. NT-proBNP could be a novel marker for differential diagnosis and prognosis of pulmonary embolism.

P2980 CTnI as the leading parameter for therapy in patients with acute pulmonary embolism in Goldhabers group II

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Introductions: In patients with acute pulmonary embolism (PE), impairment of right ventricular function is correlated to the extent of the embolic process. Mortality is increased in patients (pts) with massive PE. However, simple serologic markers for the extent of PE are still lacking. The aim of this study was to investigate the clinical and prognostic significance of sensitive and specific serum parameter of (right ventricular) myocardial damage cardiac troponin I (cTnI) in pts with acute PE. Threshold value indicating myocardial damage was 0.4ng/ml for cTnI.
Method: We prospectively investigated 40 pts with acute PE confirmed by positive d-dimer and computed tomography. Venous blood samples were drawn initially and after 6,12, 36, 24, 30, 36, 42 and 48 hours following admission for the investigation of serum parameters measured by routine laboratory methods. Right ventricular function was assessed by echocardiography (echo). Exclusion criteria were duration since the last acute event of embolism more than 48 hours, outdoor resuscitation, high grade coronary artery disease (>50% diameter stenosis), recent myocardial infarction, suspected chronic thromboembolic pulmonary hypertension or renal insufficiency with creatinine above 2.0 mg/dl.
Results: All pts were classified for the extend of PE in regard to the Goldhaber-Classification, 8 pts (20.%) were normotensive without signs of RV-dysfunction according to Goldhaber grade I (all pts cTnI neg), 21 pts (52.5%) were normotensiv without catecholamines but had RV-dysfunction on echo according to Goldhaber II (5 pts cTnI neg., 16 pts cTnI pos), 11 pts (27.5%) presented hemodynamic unstable with hypotension and need for inotropic support according to Goldhaber grade III (all pts cTnI pos). CTnI is correlated to an impaired RV function in patients with acute PE as assessed by echo (RVEDD in pos. cTnI 41.41mm ± 1.3 vs. 36.41mm ± 1.38 in cTnI neg. pts, $p<0.05$). 30-days-mortality was significantly increased in pts with acute PE and positive cTnI (37.04%) whereas non of the cTnI negative pts died ($p<0.02$). Thrombolysis and/or surgical embolectomy ($p<0.01$) as well as inotropic support ($p=0.035$) were significantly more often performed in cTnI-positive pts compared to cTnI-negative pts.
Conclusions: CTnI is qualified for the early discrimination of severity and a good predictor of mortality in PE. Especially under the consideration that non of the patients with negative cTnI died it seems to be a good screening parameter, e.g. patients of Goldhaber group II with negative cTnI don't need thrombolysis or embolectomy.

P2981 Troponin I elevation as a marker of right ventricular dysfunction and severity in pulmonary embolism

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Background: Cardiac troponin I (Ti) is a specific marker which allows the detection of minor myocardial cell damage. In patients (pts) with severe pulmonary embolism (PE), the rise in pulmonary artery pressure can lead to a progressive right ventricular dysfunction (RVD) and clinical studies demonstrated the presence of ischemia and even right ventricular infarction. **Aims:** Our aims were to determine the prevalence and diagnostic utility of Ti in identifying pts with RVD and ascertain if it correlates with the severity of PE. **Methods:** We studied 77 pts with PE diagnosed by pulmonary angiography, ventilation-perfusion lung scan, spiral computed tomography scan or by a combination of abnormal echocardiogram with clinical presentation suggestive of PE or with positive subsidiary exams (d-dimers, venous doppler of the lower limbs, EKG, blood gas analysis). We further classified the PE in severity levels, according to the European Society of Cardiology, being the PE: 1- massive, if there was shock and/or hypotension, 2- submassive, if we found right ventricular hypokinesis on the echocardiogram, and 3- non-massive, in the remaining cases. We considered the highest Ti serum value since the admission until 24 hours and a normal value of <0.10 ng/ml. **Results:** Among the 60 pts with Ti measurements, 42 had elevated values of Ti. Among the pts with RVD, 26 (81.3%) had increased Ti levels and only 14 pts (35%) with elevated Ti values didn't have RVD, indicating that positive Ti tests were significantly associated with RVD ($p=0.038$). The pts with positive Ti tests had an earlier beginning of symptoms (92.5 ± 152.79 vs 234.4 ± 232.47 hours, $p=0.02$) and a higher prevalence of emboli in proximal vessels (pulmonary trunk and right or left main pulmonary arteries) (92.0% vs 50.0%, $p=0.012$) than those with normal Ti tests. The mean level of Ti among pts with severe PE (1.65±4.27 ng/ml) was significantly higher than in those with submassive PE (1.06±0.97 ng/ml), which in turn was higher than in those with non-massive PE (0.53±0.74 ng/ml) ($p=0.045$). This gradual relationship didn't exist with the levels of d-dimers nor with the levels of systolic pressure of the pulmonary artery.
Conclusions: Around 55% of pts with PE have elevated Ti values and this test is significantly associated with RVD. Ti measurements provide additional information in the evaluation of pts with PE by the identification of pts of greater severity and at increased risk of hemodynamic deterioration, which can benefit of more aggressive therapeutical strategies.

P2982 Haemostatic and inflammatory markers in atherothrombosis of central pumonary arteries

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Some patients (pts) with chronic obstructive pulmonary disease (COPD) show at transesophageal echocardiography (TEE) stratified atherothrombotic lesions (AL) within central pulmonary arteries (CPA) in the absence of previous pulmonary embolism (PE) or significant increase in pulmonary artery systolic pressure (PAPS). We investigated the relation between TEE evidence of CPA AL and a thrombogenic or inflammatory substrate in 40 consecutive pulmonary or cardiac patients (20 with COPD, 14 with nonischemic dilated cardiomyopathy [DCM], and 6 with mitral valve disease [MVD]; mean age: 69±9 yrs), without a history of PE and showing PAPS <45mmHg at transthoracic Doppler echocardiography. Pts with venous thrombosis, neoplastic, hematologic, acute or chronic inflammatory disease, ischemic heart disease, carotid or peripheral arteries disease, or actually smoking were excluded. There were 14 pts with CPA AL (35%)(8 with COPD, 4 with DCM, and 3 with MVD) and 26 without (75%). There were no differences in age (69 vs 70 yrs), gender (60% vs 73% male), PAPS (36±8 vs 38±7mmHg), systolic blood pressure (131±16 vs 126±15mmHg), total cholesterol (C) (195 vs 191mg/dl), LDL-C (134 vs 139mg/dl), HDL-C (48 vs 49mg/dl), triglycerides (165 vs 162mg/dl), prevalence of atrial fibrillation (50% vs 34%), diabetes (28% vs 23%) and hypertension (43% vs 32%) between pts with and without CPA AL. Also, there were no differences in platelets and white-cell counts, hematocrit (38% vs 41%), antithrombin III (97±12% vs 94±14%), protein C (91±28% vs 90±37%) and protein S (89±28% vs 81±22%) activity, prevalence of factor V Leiden (3.8% vs 3.8%) and protrombin gene 20210A mutation (7.1% vs 3.8%), and plasma levels of fibrinogen (353±135 vs 363±75mg/dl) and homocysteine (10.6±3.7 vs 10.7±4.6μmol/l). Nephelometric C-reactive protein concentration was however significantly higher in pts with CPA AL (1.44±1.2mg/dl) than in those without (0.68±0.61mg/dl) ($p<0.05$). Conclusions: 1) CPA AL are a relatively frequent TEE finding in pts with pulmonary or cardiac disease presenting without severe pulmonary hypertension; 2) in these patients, CPA AL may be related to an inflammatory substrate.

P2983 Efficiency of plasma D-dimer ELISA depends on localisation of pulmonary embolism

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Background: The diagnosis of pulmonary embolism (PE) remains difficult despite new imaging and non-imaging techniques. An abnormally elevated level of plasma D-dimer ELISA has more than 90 per cent sensitivity for identifying patients with PE The aim of this study was to determine if plasma D-dimer ELISA has the same efficiency whatever the localisation of PE.
Methods and Results: We studied 42 patients (mean age 57 ± 16 years, 43% women) presenting with PE quantified by angiographic Miller index (MI). The measurement of plasma D-dimer ELISA was performed for all patients. The localisation of PE was proximal in 9 patients (21%), lobar in 21 patients (50%) or distal (12 patients, 29%). Mean MI was 43 ± 4%. Plasma D-dimer ELISA was elevated (> 500 ng/ml) in 39 patients (93%). Only 3 patients had normal D-dimer (< 500 ng/ml). For these 3 patients, mean MI was 22 ± 11% with exclusive distal PE localisation. All patients with proximal or lobar PE had elevated plasma D-dimer ELISA even when in patients with distal PE, 25% had normal D-dimer (p = 0.004).
Conclusion: Our data suggest that plasma D-dimer ELISA fails to detect 25% of distal PE.

P2984 Evidence of pulmonary vascular dysfunction from cardiopulmonary exercise testing in experimental hyperhomocystinaemia

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RATIONALE: We have shown that elevated plasma levels of homocysteine induced by methionine loading cause endothelial dysfunction in the systemic vasculature. We hypothesized that a similar effect would occur in the pulmonary vascular bed, increasing physiological dead space. Such an effect would be detectable by non-invasive cardiopulmonary exercise testing.
Methods: Ten men aged 22-31 years took part in a randomized, placebo-controlled, operator-blinded crossover study. Methionine 100 mg/kg or placebo was administered orally on two occasions a mean of 16 days apart. Blood was drawn before, and 4 hours after administration, for total Homocysteine (tHcy) levels. Subjects then carried out a maximal cardiopulmonary exercise test on a bicycle ergometer, starting at a workrate(WR) of 30Watts(W) and increasing by 20W/min. Standard cardiopulmonary parameters were measured.
Results: tHcy rose from 11.8 ± 3.1 (mean ± Std Dev) to 31.2 ± 10.3 μmol/ml ($p<0.0001$) after methionine administration, and did not rise with placebo. Exercise time, Peak oxygen consumption(PVO2), VO2/WR slope, O2pulse, Tidal volume(VT) and Minute Ventilation(VE) at peak exercise were similar in the two tests. Carbon dioxide production (VCO2), Respiratory exchange ratio(R), Endtidal CO2(PetCO2) were lower and VE/VCO2 higher at peak exercise in the Methionine-loaded tests.

Table 1: Peak Exercise gas exchange data

Test	VO2(ml/min)	VCO2(ml/min)	R	PetCO2(mmHg)	VE/VCO2
Placebo	3267 (607)	3904 (667)*	1.20 (0.05)**	37 (3)**	29.9 (2.8)*
Methionine	3152(450)	3571 (462)*	1.13 (0.05)**	34 (4)**	32.2 (4.6)*

Data shown as Mean (Std Dev). *$p<0.05$, **$p<0.01$ by paired Student T-Test

Conclusions: The differences in VE/VCO2 between the two tests, while small, are significant and are consistent with either hyperventilation, or a degree of Ventilation/Perfusion mismatch with methionine. The lower R and VCO2 are against hyperventilation. These data suggest that experimental hyperhomocystinaemia impairs pulmonary vascular function.

P2985 Prognostic value of echocardiography in massive and submassive pulmonary embolism: a retrospective study of 624 patients

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Right ventricular dilation induced by massive and submassive pulmonary embolism (PE) can be easily detected, at bedside, by echocardiography (EC). To test the prognostic value of this parameter, we retrospectively analyzed a population of 624 consecutive patients admitted to our institution for acute massive or submassive PE, and who were evaluated by EC at baseline.
Results: Right ventricle/left ventricle end diastolic diameter ratio (RV/LV) was calculated from the long axis parasternal view, the subcostal view or the apical 4 chamber view. 23 pts died during the index hospitalization (3.7%). Univariate analysis revealed that among 8 parameters, only the signs of shock, the perfusion lung scan (LS) defect and RV/LV were significantly associated with the risk of death (see table).

Univariate analysis of risk factors

	Death	Alive	p
	n=23	n=601	
Age (95% CI)	72 (65-78)	71 (69-72)	0.37
Gender (M/F) (n)	8/15	263/338	0.39
Previous TE (n)	7	228	0.46
CI to thrombolysis (n)	11	211	0.21
Thrombolysis (n)	9	136	0.07
RV/LV (95% CI)	0.99 (0.79-1.20)	0.70 (0.68-0.72)	< 0.0001
LS defect % (95% CI)	50 (45-55)	39 (38-40)	0.001
Shock (n)	8	53	0.0001

(CI = contra-indication, TE = thromboembolism)

After adjustement to shock, LS defect and thrombolysis, RV/LV appeared as an independent predictor of death (p=0.04) in multivariate analysis.
Conclusion: the results of this study indicate that an aggressive therapy should be considered in patients suffering from acute PE when RV/LV >= 0.8, even in the absence of signs of shock.

P2986 Nitric oxide inhalation modulates circulating endothelin-1 after left ventricular assist device implantation

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Nitric oxide inhalation is an established therapy in the treatment of secondary pulmonary hypertension after left ventricular assist device (LVAD) implantation. As a selective pulmonary vasodilator inhaled nitric oxide (iNO) decreases right ventricular afterload without systemic hypotension. Endothelin-1 (ET-1) as a potent endogenous vasoconstrictor contributes to pulmonary hypertension and NO modulates the ET-1 synthesis in vitro. The effects of iNO on circulating ET-1 and big endothelin (big ET-1) in LVAD-patients were investigated.
Methods: On weaning from cardiopulmonary bypass (CPB) 15 patients with right ventricular dysfunction were treated with iNO. Plasma ET-1 and big ET-1 concentrations were measured preoperatively, on CPB prior to iNO, 12, 24, and 48 hrs. postoperatively, as well as 72 hrs after cessation of iNO.
Results: Mean initial iNO dose was 33 ppm. NO therapy was weaned in all patients without a rebound phenomenon. ET-1 and big ET-1 were increased preoperatively (1.22±0.17 and 3.64±0.71 fmol/ml, respectively). ET-1 concentrations were highest on cardiopulmonary bypass (1.40±0.18 fmol/ml).
ET-1 and big ET-1 decreased significantly during iNO therapy and were lowest 72 hrs after cessation of iNO (Table). The iNO dose and plasma ET-1 levels correlated significantly ($p<0.001$). A significant correlation was also found between ET-1, PA-pressures and PVR, but not with CI and SVR.

Plasma concentration-time profile

	12h	24h	48h	72h post NO
ET-1 (fmol/L)	1.17±0.17	0.94±0.2	0.72±0.14	0.48±0.09
big ET-1 (fmol/L)	5.49±1.13	3.64±0.49	4.12±0.93	2.18±0.23

Conclusion: Since it is known, that ET-1 mediates pulmonary hypertension, we suggest a two-fold effect of iNO therapy: first a selective vasodilation of the pulmonary vasculature and second NO-mediated inhibition of one of the most potent vasoconstrictors of pulmonary vessels: ET-1.

P2987 Serotonin receptor blockade improves monocrotaline-induced pulmonary hypertension and prolongs survival in rats

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It has been reported that platelet activity is enhanced with increased plasma levels of serotonin and P-selectin in pulmonary arterial hypertension. The present study was designed to assess the effects of serotonin receptor blockade on monocrotaline (MCT)-induced pulmonary hypertension (PH) and survival in rats. Rats were randomized to receive MCT (40mg/kg, SC) followed by placebo (group A) or sarpogrelate, a serotonin receptor blocker (50mg/kg, IP) (group B) for 3 weeks. Immunohistochemical staining for P-selectin, CD45, endothelial nitric oxide synthase (eNOS), and proliferating cell nuclear antigen (PCNA) were performed. In group A, there were marked expression of P-selection and CD45-positive leukocytes adhered to the P-selectin-expressing cells and platelets on the endothelial cells of pulmonary arterioles and venules in association with severe pulmonary hypertension, muscularization of the pulmonary arteries, and right ventricular hypertrophy. In addition, expression of eNOS on the pulmonary arteries was significantly decreased and the number of PCNA-positive cells was increased in group A compared with those of the normal control animals. These inflammatory processes, endothelial injury with impaired NO/O2- balance, and functional and structural abnormalities of the pulmonary vessels were markedly suppressed in group B. At 3 weeks after treatment, survival rate in group B was 87% compared with 40% in group A ($p < 0.05$). In conclusion, serotonin receptor blockade with sarpogrelate improves MCT-induced PH and prolongs survival in rats, which was mediated by suppression of endothelial injury, enhanced platelet activity, inflammatory responses, and proliferation of the pulmonary vascular smooth muscle cells and improved NO expression of the pulmonary vessels in this model.

P2988 Prognostic significance of cardiac pulmonary exercise testing in pulmonary arterial hypertension

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Cardiopulmonary exercise testing (CPET) is a useful noninvasive tool to assess functional capacity and the physiological changes associated with exercise. Patients (pts) with pulmonary arterial hypertension (PAH) have a unique response due to the combined manifestations of cardiac, pulmonary and peripheral limitations characterized by this disease. Although the prognostic significance of CPET in CHF pts is known, the objective of this study was to assess the usefulness of CPET in PAH pts. Hence, 90 consecutive patients underwent testing at baseline and after one year of treatment with chronic intravenous prostacyclin (PGI2).

To address the question of CPET as a useful surrogate endpoint, we analyzed the effects at baseline, at 1 year follow-up (f/u) and change from baseline to 1 yr. f/u (delta) of VO2, Ve/VCO2, 6-minute walk and PAPm on survival data utilizing a proportional hazard regression.

Data showed: 1) PGI2 therapy was associated with a significant improvement ($p<0.05$)in all exercise and hemodynamic parameters (table). 2) Both f/u and delta VO2 are good predictors of survival. 3) Baseline and f/u 6-minute walk are independently good predictors of survival. 4) Baseline and f/u Ve/VCO2 but not delta are independently good predictors of survival. 5) Both f/u and delta PAPm values are independently good predictors of survival.

Parameters at baseline and follow up

	Baseline	Follow up (1 yr.) on PGI2	p value
VO2 (ml/kg/min)	13.1 ± 0.6	16.9 ± 0.6	<.0005
Workload (watts)	38.0 ± 2.3	55.5 ± 3.1	<.0005
Ve/VCO2	55.7 ± 2.1	46.7 ± 1.3	<.0005
6-minute walk (m)	394.9 ± 14.6	472.4 ± 11.3	<.0005
PAPm (mm Hg)	65.4 ± 1.7	50.5 ± 1.7	<.0005

paired t-test (mean ± SEM)

Conclusion: Both 1 yr. f/u and delta VO2 and PAPm, which likely best represent treatment effects, predict survival. Baseline and 1 yr. f/u 6-min. walk and Ve/VCO2 are good predictors of survival but possibly are less sensitive to treatment effects. Thus, CPET is useful to predict survival in PAH.

P2989 Non-invasive assessment of mean and systolic pulmonary artery pression in athletes: a stress-echo study

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Background: Doppler transtoracic echocardiography (TTE) has been validated for estimation of mean and systolic pulmonary artery pressure (PAP). Mean PAP can be evaluated in all subjects from time to peak velocity in pulmonary artery. Systolic PAP can be estimated in subjects with tricuspid regurgitation (TR) by Doppler evaluation of TR peak velocity (TRV). Rest TRV <2,5 has been reported as the upper limit in normals. At present, the whoole range of rest and exercise TRV and mean PAP in athletes is not yet completly defined.
Objectives: The aim of the study was to estabilish, in athletes, a reference range for mean pulmonary artery pression and tricuspid regurgitation velocity at rest and during exercise.
Materials and Methods: Doppler echocardiographic study was obteined in 428 conditioned athletes (mean age: 38,5±19,1) and 233 healthy sedentary subjects (mean age: 33±12) both at rest and during standardized recumbent bicycle exercise. Mean PAP was estimated in all subjects, both at rest and during stress test. TRV and systolic PAP were evaluated in a subgroup of subjects, randomized within those with detectable TR (70 athletes and 70 controls).
Results: Left ventricular dimensions and mass were significant greater in athletes than in controls; no significant differences were found in rigth atrium and ventricular dimensions between the two groups. Rest mean PAP was significantly lower in athletes than in controls (16,3±3,8 mmHg in athletes; 17,2±4,2 mmHg in controls); no significant differences were found in exercise mean PAP between athletes and controls. No significant differences were found in rest and exercise TRV between athletes and controls (2,1±0,4 -2,8±0,4 in athletes; 2,1±0,4 -2,7±0,6 in controls), that is that no differences were found in rest and exercise systolic PAP in the two study groups (28,3±6- 41,9± 10,1 mmHg in athletes; 29,3±7,3 - 38,9± 14,5 in controls).
Conclusions: This study indicates the normal range of TRV, systolic and mean PAP in a large athletes' population.

P2990 Assessment of dynamic changes in perfusion lung scintigrams in patients with CTEPH

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Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is the result of single or recurrent pulmonary thromboemboli arising from sites of venous thrombosis. Over time thrombi become organized obstructions that are thought to expand by recurrent embolisation and in situ thrombosis. We performed a quantitative evaluation of ventilation and perfusion scintigrams (V/Q scan) in patients with inoperable CTEPH in order to assess the natural history of thrombus expansion.
Methods: We prospectively studied 11 CTEPH patients (52±11years, 7 females, 4 males) over a period of 28 months. The baseline V/Q scan was obtained at the time of diagnosis. Ventilation imaging used [99mTc] DTPA aerosol and perfusion imaging was performed with intravenous [99mTc]-labeled human albumin macroaggregates. Planar images were reconstructed in eight standard projections. The right lung (RL) and the left lung (LL) were subdivided into an upper, middle and lower region of interest (ROI). The ratio of the mean count per pixel in the ROI to the count over the heart was calculated as the Lung/Heart index (L/H). The RL and LL variation coefficient (Vc), i.e. the ratio of the count standard deviation and the average count of the ROI were evaluated from the same planar scintigrams. Student's paired t-test was used to analyze baseline and follow up data.
Results: During the observation period, mean pulmonary artery pressure increased from 48.4±14.6 to 54.7±8.1mm Hg, PVR increased from 9.8±4.6 to 10.9±4.0 Wood Units. All L/H indices increased over time. For example, baseline right middle ROI was 6.9±2.1 compared with follow up right middle ROI of 9.4±2.5 (P=0.0024), and the baseline right upper ROI was 4.2±1.5 compared with right upper ROI at follow up of 6.5±2.4 (P=0.0083). The baseline Vc was 51.7±8.0 (LL), 58.5±7.4 (RL). The follow-up Vc was 44.4±8.4 (LL) and 45.5±8.2 (RL, p=0.0017).
Conclusions: In parallel with hemodynamic deterioration,lung perfusion scintigrams in patients with inoperable CTEPH show a decrease of segmental flow abnormalities. We speculate that, over time, secondary vascular changes determine the course of CTEPH and ultimately lead into the scintigraphic pattern of nonthromboembolic pulmonary hypertension.

P2991 Screening for early pulmonary hypertension in patients with systemic sclerosis: is an aggressive invasive approach required?

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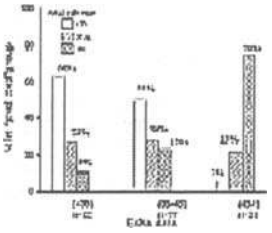
Aim: To document the accuracy of echo to identify early PHT in a high-risk SSc cohort.
Background: From 950 patients under regular follow-up, dyspnoeic patients with a echo-estimated tricuspid gradient (TG)>35 mmHg/those with TG<35 mmHg with dyspnoea unexplained by the presence of pulmonary fibrosis/ and those with DLCO<50% predicted were catheterised
Method: Echo and catheter measured TGs were correlated. A linear regression was derived to predict catheter-measured mean Pulmonary Artery Pressures(mPAPs)from echo estimated TGs.
Results: Out of the 140 patients studied (F: M≈119:21),mean age=56±7 years. Haemodynamics: mPA Sys=47mmHg, mPA diastolic=18 mmHg, mPAP=34 mmHg, mRAP=4 mmHg, mean echo estimated TG=42 mmHg.
Echo-estimated TG showed a positive correlation with catheter-measured TGs(r2=0.44, p<0.005).
By linear regression(figure),echo was sufficiently accurate at moderate/ high pressures (echo TG>45 mmHg) identifying>80% of patients correctly.At lower pressures where early diagnosis is critical, echo was less discriminatory- it both under/over-estimated the catheter-measured mPAPs in 30% of cases.This may lead to over-diagnosis of PHT in unaffected patients.



Cath. mPAP versus echo TG.

Conclusions Though echo accurately identified a poor prognostic group(mPAP>35 mmHg on cardiac catheter), reliance on echo to accurately identify early PHT in "at risk" SSc patients is inadequate. In its current form, echo-estimated TGs demonstrate a tendency to both under and over-estimation at the lower end of the spectrum - with the subsequent risk of exposing a patient with either no or mildly elevated pulmonary pressures to over-investigation. This latter finding is particularly relevant when applied to low prevalence PHT populations where the false positive rates are proportionately higher.

MYOCARDIAL ISCHAEMIA/INFARCTION

P2992 Value of right derivation records in treadmill test taken simultaneously with standard left derivations in the diagnosis ischaemia

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Treadmill test is a common test used in the diagnosis of ischemic heart disease with a diagnostic sensitivity of 65-70%. We have evaluated the sensibility and diagnostic value of right derivations records taken simultaneously with standard left derivartions in this study.
Methods: 74 consecutive patients (30 women, 44 men, mean age 54.6±10.2 years) who were referred to our nuclear cardiology laboratory for the evaluation of chest pain were included in our study. Our exclusion criteria were previous revascularization procedure (ACBG, PTCA), bundle branch block or left ventricular hypertrophy. All patients were evaluated by exercise myocardial perfusion scintigraphy (MPS) and coronary angiograms (CA). 3 right precordial derivations (V3R, V4R, V5R) were recorded simultaneously with the standard 12 derivations during exercise. Ischemia was diagnosed as 1 mm ST depression. Sensitivity, specivity, (+) and (-) predictive value and accuracy of the tests using both standard and right derivations were estimated. Positive results were taken as a temporary perfusion defect on MPS or a coronary artery lesion greater than 70% detected by CA. 32 pts had coronary artery disease detected by MPS or CA.
Results: 30 pts had ischemic changes during exercise when evaluated by standard exercise test. In 21 of these pts, coronary artery disease was detected by MPS or CA. 11 out of 44 pts without ischemia had coronary artery disease detected by MPS or CA. Sensitivity, specivity, (+) and (-) predictive value and accuracy were calculated as 66%, 79%, 70%, 75% and 73% respectively. When right derivations were taken with the standard derivations, 21 pts had coronary artery disease out of 36 pts who had ischemia on exercise test. Only 8 pts out of 38 pts without ischemia had a perfusion defect on MPS and CA. Sensitivity, specivity, (+) and (-) predictive value and accuracy were calculated as 88, 81, 80, 90 and 84 respectively. Addition of right derivations to standard derivations has resulted in statistically significant increase in the sensitivity of the test (p=0.037) whereas specivity did not change.
Conclusion: Addition of right derivations to standard derivations during exercise test increases the sensitivity of the test in the diagnosis of ischemia.

P2993 Acute renal failure complicating first myocardial infarction: the impact on infarct course and in-hospital mortality

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Aim: Acute renal failure (ARF) is a major cause of in-hospital morbidity and mortality, usually indicating the serious nature of the underlying disease. ARF complicates approximately 5% of hospital admissions and up to 30% of admissions to intensive care units. The aim of this study was to investigate the incidence of ARF in patients with first acute myocardial infarction (AMI), reveal the influencing factors and assess it's impact on infarct course and final outcome.
Methods: We analyzed renal function in 583 patients with first AMI (363 or 62.3% male, mean age 66.7±12.9 years), admitted to our Coronary Care Unit from January 1, 2000 to June 30, 2001. Diagnosis of ARF was based on serum creatinine levels, i.e. acute increase in creatinine from normal to above 180 μmol/L, or it's rise from baseline values for 50% or more in patients with previous mild to moderate renal failure.
Results: In 58 (9.9%) patients (34 male, 24 female, mean age 74.9±8.1 years) AMI was complicated with ARF. The causes of ARF were acute heart failure (31 pts, 53.5%), adverse drug effects (7 pts, 12.1%), transient hypotension due to volume depletion (5 pts, 8.6%), or combination of the previous causes (15 pts, 25.8%). ARF occurred more frequently in patients over 65 years (13.6% vs. 3.3%, p<0.05), diabetics (36.5% vs. 13.6%, p<0,05), hypertensive patients (12.9% vs. 4.5%, p<0.05) and those with acute heart failure (22.1% vs. 4.7%, p<0.05). Patients with ARF complicating first AMI had longer hospitalisation (19±12 vs. 12±5 days, p<0.05) and higher mortality rate (50.0% vs. 11.2%, p<0.05). Significant difference in mean maximal serum creatinine existed between 25 oliguric (43%) and 33 non-oliguric (57%) ARF patients (283±87 vs. 205±45 μmol/L, p<0.05). When compared to non-oliguric group, oliguric patients recovered renal function to baseline creatinine levels less frequently (8.0% vs. 57.6%, p<0.05), and had the highest mortality rate (76.0% vs. 30.3%, p<0.05).
Conclusion: The results indicate that ARF in first AMI occurs more frequently in older population, patients with acute heart failure, diabetes mellitus and hypertension. AMI patients with ARF need prolonged hospital stay, have more serious infarct course and significantly higher mortality, specially those oliguric.

P2994 Clinical characteristics of systemic embolization in acute myocardial infarction

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The frequency, risk factors and prognostic significance of systemic embolism (SE) were studied in acute myocardial infarction (AMI). Data on 1833 patients with Q-wave AMI treated at the County Hospital, Eger, during a 10-year period were analyzed. During the hospital treatment, 53 patients (2.9%) developed SE, localized as follows: 38 cerebral, 7 extremital, 3 renal and 5 multiple. The diagnosis of SE was based on the clinical symptoms, pathological findings and/or radiological examinations. The embolic events occurred most frequently (70%) in the first 72 hours of AMI. In 5 cases the SE was the first clinical manifestation of the AMI. The characteristics of the different clinical groups (AMI+SE vs. AMI alone) are summarized in the table.

	AMI+SE (n=53)	AMI without SE (n=1780)	p value
Age (years)	70.1	63.9	<0.001
Men (%)	57	64	NS
Smoking (%)	26	34	NS
Diabetes (%)	25	21	NS
Hypertension (%)	60	60	NS
Hypercholesterolemia (%)	38	45	NS
Previous MI (%)	9	12	NS
Anterior MI (%)	58	41	=0.02
Atrial fibrillation (%)	15	10	NS
Thrombolytic therapy (%)	6	22	<0.01
LV aneurysm (%)	17	8	<0.05
LV dilatation (Dd>60 mm; %)	33	20	NS
LV ejection fraction<40% (%)	25	17	NS
LV thrombus	36	7	<0.001
Hospital mortality	30	9	<0.001

Conclusions: SE is a rare and severe complication of AMI. The patients in whom SE developed were older and thrombolytic therapy was administered less frequently. On the other hand, an anterior AMI, a left ventricular aneurysm and thrombus formation were significantly more frequent in the AMI+SE group.

P2995 Predictors of new onset atrial fibrillation in patients presenting with acute coronary syndromes and their in-hospital outcomes

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Background: Predictors of new onset atrial fibrillation (AF) in unselected patients with acute coronary syndromes (ACS) and their outcomes have not been studied.

Methods: Accordingly, we evaluated 14,556 patients with ACS enrolled in the Global Registry of Acute Coronary Events (GRACE) between 1997 and 2000.

Results: New onset AF occurred in 908/14556 (6.2%) of ACS patients. Multivariable logistic regression analysis identified older age (per 10 year increase Odds ratio [OR] 1.65, 95% confidence interval [CI] 1.55-1.75), female gender (OR 1.20, 95% CI 1.03-1.40), heart rate (per 30 beats/minute increase, OR 1.79, 95% CI 1.65-1.96), ST elevation MI (referent unstable angina, OR 2.18, 95% CI 1.79-2.66), Non-ST elevation MI (referent unstable angina, OR 2.08, 95% CI 1.71-2.54) and cardiac arrest on presentation (OR 1.77, 95% CI 1.20-2.61) to be associated with an increased risk of AF. In contrast, prior revascularization (OR 0.74, 95% CI 0.60-0.90) and higher systolic blood pressure (per 20 mm Hg increment, OR 0.87, 95% CI 0.83-0.91) were associated with a lower risk of AF (Model c-statistics 0.75, Hosmer and Lemeshow Goodness-of-Fit p=0.14). Most comorbid conditions occurred with an increased frequency among ACS patients with AF. However, even after adjustment for the differences in baseline clinical characteristics, AF remained an important predictor of most adverse in-hospital events (table).

Odds ratio for in-hospital events

Outcome	Odds ratio-Adjusted	95% confidence interval	p value
Death	3.16	2.01, 4.95	<0.0001
Re-infarction	2.07	1.01, 4.27	0.048
Cardiogenic shock	3.61	2.24, 5.82	<0.0001
Pulmonary edema	3.95	2.54, 6.13	<0.0001
Cardiac arrest	3.21	2.01, 5.14	<0.0001
Stroke	0.61	0.13, 2.76	0.519
Major bleeding	1.78	1.06, 2.98	0.029

Conclusions: Our study helps identification of ACS patients at risk for AF who may benefit from early aggressive strategies to modify the increased risk of adverse in-hospital events observed among these patients.

P2996 Atrial fibrillation in high risk patients with acute myocardial infarction: data from the MISTRAL study

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Background: Atrial fibrillation (AF) is a common complication of acute myocardial infarction (AMI). We observed the prevalence, clinical factors associated with its presentation and association with patient outcome in high risk (HR) pts with AMI in a community setting.

Methods and Results: 2227 pts with ST elevation AMI <12 h were recruited having >=1 of the following characteristics identifying HR: female >70 y (17.8%), diabetic >70 y (9%), Killip class >1 (23.7%), systolic blood pressure (SBP) <100 mmHg and heart rate >100 b/m (2.7%), >4 leads with ST elevation or depression (81.9%), previous Q-wave MI in another location (11.4%), contraindication to TT (10.2%).

AF was documented in 272 pts (12.2%). Pts with AF were significantly older (>70 yrs, 64% vs 32%, p<0.001), more likely to be female (43% vs 26%, p<0.001), with a higher Killip class at entry (Killip >1, 37% vs 22%, p<0.001), incidence of heart failure or cardiogenic shock during hospitalization (44% vs 23%, p<0.001) and probability to not receive reperfusion therapy (31% vs 17%, p<0.001).

At univariate analysis AF patients had higher in-hospital mortality (18.4% vs 9.1%, p<0.001) and a more frequent in-hospital combined end-point (in-hospital death, non fatal re-AMI and stroke) (21% vs 11%, p<0.001). At 1 year follow up both total mortality and 1-year combined end-point were more frequent in pts with AF than those without AF (29.8% vs 14.9%, p<0.001; 38.9% vs 19.6%, p<0.001, respectively).

Multivariate analysis indicated the most significant predictors of the development of AF were advanced age (OR 1.07, 95%CI 1.05 -1.09) and Killip class >1 (OR 1.44, 95%CI 1.06-1.95).

At multivariate analysis, after adjustment for clinical and demographic factors, the association between AF and in-hospital and 1-year mortality was no longer statistically significant (OR 1.02, 95%CI 0.67-1.54; OR 1.41, 95%CI 1.06-1.88, respectively). Similarly, the association between AF and in-hospital and 1-year combined end-point disappeared (OR 1.06, 95%CI 0.73-1.56; OR 1.32, 95%CI 0.95-1.83, respectively).

Conclusions: In HR pts with AMI the most significant predictors of the development of AF were advanced age and clinical severity of AMI. Differently from other studies, in this class of pts AF was not an independent predictor of mortality.

P2997 Underuse of new treatment modalities in diabetics with non-ST-segment elevation acute coronary syndrome

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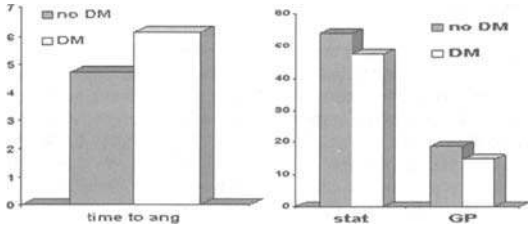
In last years our knowledge about risk stratification and treatment strategies of patients with acute coronary syndrome(ACS) without ST-elevation has increased rapidly and new guidelines have been published. It is not clear how these new guidelines have been implementated into clinical practice.
We prospectively collected all ACS patients without ST-elevation admitted in 9 hospitals in Finland during 1-3/2001, followed practice patterns and outcomes during hospitalization and at 6 months follow-up.
A total of 501 patients were entered into the survey, from which 143 (28.5%) had diabetes. Diabetics were older 71±10 vs 67±12;p<0.0001, had more treated hypertension 66% vs 48%;p<0.0001 and more peripheral vascular disease 30% vs 9%;p<0.0001 when compared to nondiabetics. Diabetics had higher risk profile than nondiabetics; ST-depression 57% vs 38%;p<0.0001, elevated troponin levels 66% vs 56%;p<0.05. Despite that the rate of in-hospital angiography was lower in diabetics than nondiabetics (32% vs 45%;p<0.05). Diabetics also waited more days for in-hospital angiography than nondiabetics(figure). In-hospital use of glykoprotein IIb/IIIa(GP) inhibitors and statins(stat) were lower in diabetics than nondiabetics (figure). At 6 months the rates of death were 16% and 7.6%;p<0.01 in diabetics and nondiabetics respectively. For the combination of death, myocardial infarction, refractory angina or readmission for unstable angina, rates of events were 38.5% vs 20%;p<0.0001, respectively.



Diabetics had higher risk profile than nondiabetics. Despite that the use of in-hospital angiography, statins and GP inhibitors were lower in diabetics than nondiabetics. Further education is needed to implementate the new guidelines into the clinical practice.

P2998 Early revascularisation for non-ST-segment elevation acute coronary syndromes: an estimation of demand in the UK

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Background: The current ESC guidelines for the management of non-ST-elevation acute coronary syndrome (NSTEACS), recommend that patients at high risk of an adverse outcome should undergo coronary angiography and, where possible, revascularisation during their initial hospitalisation. We performed a prospective observational study to determine the likely size of the demand for early revascularisation therapy for NSTEACS in a large UK teaching hospital.
Methods: All emergency admissions to our hospital because of suspected unstable angina or myocardial infarction during the year 2000 were identified at presentation, using 'hot pursuit' methodology. Patients were excluded if their initial electrocardiograms showed persistent ST segment elevation or if they had already been included in the study. For each patient data were recorded on demography, clinical presentation and risk factors, ECG appearances, serum biomarkers levels and outcomes. The study population was then risk stratified according to ECS recommendations and an estimate made of the likely need for early revascularisation.
Results: 2098 patients were included in the study. 891 (42.5%) satisfied ESC criteria for high-risk status. Of these, 659 (74.0%) had elevated troponin levels, 199 (22.3%) developed recurrent ischaemia and 160 (18.0%) had unstable angina soon after a recent myocardial infarction.
Discussion: If the ESC recommendations on the management of NSTEACS are applied to a typical unselected population of patients admitted to a large UK hospital, the demand for early revascularisation will far exceed current service provision. The same is likely to be true for other UK hospitals.

P2999 Emergency electrocardiogram analysis during the acute phase of coronary syndromes: to be improved?

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Background: ECG analysis is essential in the management of patients with acute coronary syndrome (ACS) without persistent ST segment elevation. However, little is known about the quality of this analysis in the emergency room (ER). Our study was performed to specifically answer this question.
Methods: We prospectively compared the ECG analysis performed in the ER during the acute phase of ACS with a blind assessment by an intensivist and an interventional cardiologist; discordances were then resolved by an ECG specialist. Analysis focused on the ischemic modifications (ST segment elevation and depression, negative T-waves) of the ECG.
Results: In total, 627 ECG were included. The experts assessment wasn't fully concordant (kappa 0.8 and 0.9) with the ECG specialist. Analysis in the ER were concordant with those of the experts in only 423 ECG (67%; kappa 0.4). The details are summarized in the following table:

	No modification	ST elevation	ST depression 0.5-1	ST depression >1mm	Negative T-waves
No modification	352	18	10	2	34
ST elevation	18	21	4	3	7
ST depression 0.5-1mm	43	5	15	5	8
ST depression >1mm	12	6	4	13	1
Negative T-waves	19	2	1	2	22

X: emergency phycisians interpretation; Y: experts interpretation

Conclusion: Our study demonstrates that ECG analysis in the ER during the early management of ACS is not accurate. A better ECG analysis should allow better risk stratification and management of the patients, but the impact of these discrepancies need further study.

P3000 Acute coronary syndromes in 15 young AIDS patients receiving HIV-protease inhibitors. A 3-year follow-up study

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Acute coronary syndrome (ACS) is an emerging complication in HIV-infected patients treated with highly active antiretroviral therapy (HAART) due to increase in life expectancy. HAART has been involved in metabolic disorders (MD) such as hypertriglyceridaemia (HTG), hyercholesterolemia (HCT), insulin resistance, diabetes mellitus and a syndrome of peripheral lipodystrophy. We report 15 cases of ACS (12 AMI, 3 UA) in young HIV-men associated with HAART followed during a 3 years period.

Characteristics patients		Acute phase (n=15)	
Male gender	14 (93%)	Anterior AMI	6 (40%)
Prior MI	0	Inferior AMI	7 (47%)
Age, y	42±6	Lateral AMI	2 (13%)
Current smoker	12 (80%)	3VD	4 (27%)
HCT/HTG	7 (47%)/13 (87%)	2VD	2 (13%)
HTN	2 (13%)	1VD	9 (60%)
Diabetes	0	LV thrombus	2 (13%)
Duration of HIV, y	8±4	LVEF, %	56±12
Duration PI, m	20±12	PCI	7 (47%)
CD4/mm^3	370±140	Mean FU, m	35±15
Median viral load	9300±2370	Death, AMI	1, 0
Lipodysthrophy	6 (40%)	UA, PCI, CABG	4, 3, 2

h: hours, m: months, y: years, c: copies/mL, VD: vessel disease, LVEF: left ventricular ejection fraction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, FU: follow-up.

Conclusion: Physicians should take aware of CV risks factors before initiating HAART in AIDS patients. Prospective studies of patients under HAART are needed to clarify the link between HAART and CV complications.Table

P3001 Metabolic protection with glucose-insulin-potassium infusion in patients with acute myocardial infarction. Results of the REVIVAL trial

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Background: Intravenous glucose-insulin-potassium solution (GIK) may have a positive metabolic influence in patients with acute myocardial infarction (AMI). However, previous clinical studies have shown conflicting results with this therapy. This may have been the result of the infrequent use of reperfusion therapies in those studies. In fact, there is some data suggesting that patients with AMI who receive reperfusion therapy might have a greater benefit from GIK. The objective of this randomized trial was to assess for the first time whether GIK improves myocardial salvage in patients with AMI.
Methods: We randomized 312 patients with AMI to receive either a GIK infusion for 24 hours (GIK group, n=155) or no GIK (control group, n=157). The primary endpoint of the study was salvage index (proportion of myocardium at risk salvaged by therapy) as measured by technetium Tc 99m sestamibi scintigraphic studies performed before and 7-10 days after therapy. Secondary endpoint was the composite clinical event rate of death, recurrent MI and stroke within 30 days.
Results: Primary percutaneous intervention (PCI) was the predominant reperfusion strategy (90% of the cases). There were no significant differences in the baseline characteristics of the patients of the 2 groups, including initial perfusion defect in scintigraphy. Median [25th, 75th percentiles] of final infarct size was 9.0% [2%, 20%] of the left ventricle in the GIK group and 8.5% [3%, 21%] of the left ventricle in the control group (P=0.7). The primary endpoint of salvage index was 0.50 [0.18, 0.87] in the GIK group and 0.48 [0.18, 0.87] in the control group (P=1.0). Mortality within 30-days was 4.5% in the GIK group and 3.2% in the control group (P=0.5). The combined 30-day rate of death, recurrent MI and stroke was 5.8% in the GIK and 5.1% in the control group (P=0.8).
Conclusions: GIK does not further enhance myocardial salvage in patients with acute myocardial infarction treated predominantly with PCI. This may explain the lack of clinical benefit observed in this and previous studies with GIK.

P3002 Continuous ST-segment monitoring identifies patients with acute coronary syndromes who most benefit from early myocardial revascularization

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Background: In patients with non-ST-elevation acute coronary syndromes, early risk stratification is essential for guiding cost-effective management. Continuous ST-segment monitoring adequately reflects the dynamic nature of myocardial ischemia and coronary thrombosis, and provides important prognostic information in such patients. We investigated whether continuous ST-segment monitoring may be useful for early identification of those who most benefit from myocardial revascularization.
Methods: We studied 304 patients (22% female, age 65 ± 11 years) admitted to the CCU due to chest pain at rest (at least one episode of chest pain at rest in the previous 24 hours lasting at least 20 minutes) suggestive of an acute coronary syndrome without ST segment elevation on the admission ECG. Patients whose ECG was not interpretable for ischemia were excluded. ST segment monitoring was performed continuously for 24 hours after admission. An ST episode was defined as a transient deviation of at least 0.1 mV in any lead lasting at least 1 min. In-hospital myocardial revascularization was performed at the discretion of the attending physician. The endpoint was death or nonfatal (re) myocardial infarction, whichever occurred first by 30 days follow up.
Results: A total of 203 ST episodes (135 clinically silent) were detected in 76 patients (25.0%). Myocardial revascularization was performed in 200 patients (65.8%), through percutaneous intervention in 146. Median time from admission to revascularization was between 24 and 48 hours. The detection of ST episodes was independently associated with worse 30-day outcome, even after adjustment for baseline clinical characteristics, ECG changes and cardiac troponin I levels (adjusted odds ratio 4.9; 95% CI, 1.9 to 12.9; p=0.001). In the group of patients with ST episodes, myocardial revascularization had a beneficial impact on prognosis (10.5% event rate versus 36.8% in patients not revascularized; odds ratio 0.2; 95% CI, 0.1 to 0.7; p=0.022). In the group of patients without ST episodes, the effect of myocardial revascularization was modest (2.8% event rate versus 5.9% in those not revascularized; odds ratio 0.5; 95% CI, 0.1 to 1.8; p=ns).
Conclusion: In non-ST-elevation acute coronary syndromes, continuous ST segment monitoring provides early prognostic information, additional to that of clinical characteristics and biochemical markers of myocardial injury and is useful for selection of patients who most benefit from early myocardial revascularization.

P3003 Management and predictors of 30-day events in the French registry on acute coronary syndromes without persistent ST elevation (FRACAS)

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Background: Most of the available data about acute coronary syndromes (ACS) were provided by randomised trials. We therefore sought to investigate the current management and the early outcome of ACS without ST elevation in French centres with on-site percutaneous coronary intervention (PCI) facilities.
Methods: 89 centres selected on a geographic basis were asked to complete a prospective record for 10 consecutive patients (pts) admitted in their coronary care unit for ACS without persistent ST elevation (chest pain<48 hours with ECG changes and/or myocardial damage marker elevation).
Results: 873 pts were included (mean age 65±13, male 73%). Most of the patients experienced chest pain within 12 hours prior to admission (87%) and a history of coronary artery disease was present in 51%. Following ECG changes were observed: ST depression 42%, transient ST elevation 5%, T waves abnormalities 42%. Only 13% of the pts had normal ECG. During the first 24 hours, abnormal serum cardiac markers were elevated in 40% of the pts (either CK>2ULN or Troponin>N). Initial antithrombotic regimen included a combination of heparin+antiplatelet agents in 86% with either heparin or antiplatelet agents in 99%. Initial prescription of GP IIB/IIIA inhibitors was low (8.6%). In addition, 71% of the pts were on bblockers and 70% on IV nitrates. During the index hospitalisation, coronary angiography was performed in 790 pts (90%) and coronary revascularisation in 529 pts (61%, PCI 484, CABG 45). PCI were mainly performed within 48 h following admission (55%) and the procedure included GP IIB/IIIA inhibitors infusion in 21% and stent implantation in 80%. At 1 month, 572 pts (66%) had undergone coronary revascularisation (PCI, 493, CABG 85). 30-day outcome was available in 804 pts and the predefined combined endpoint of death, Q-wave MI or refractory ischemia was noted in 10.1%. Endpoint rate according to the TIMI risk score, was, 2.8, 9.8 and 13.9% for the low, medium and high risk, respectively (p<.006). Independent predictors of an impaired outcome were: ST depression or prior Q-wave on ECG, initial CK or troponin elevation, presence of 3-vessel disease and no coronary angiogram performed as well as the TIMI risk score if entered in the model.
Conclusion: Management of ACS without persistent ST elevation in centres with on-site PCI facilities was characterised by an early invasive strategy with a high percentage of myocardial revascularisation. The early outcome was similar to that of reported in randomised trials and was easily predicted by a risk score derived from these trials.

P3004 Which stress test is superior for perioperative cardiac risk stratification in patients undergoing major vascular surgery?

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Background: Patients undergoing major vascular surgery are at increased risk of cardiac complications. Cardiac risk factors can be used in conjunction with appropriate diagnostic testing to identify high-risk patients. We explored the comparative added prognostic value of Dobutamine Stress Echocardiography (DSE), Dipyridamole Stress Echocardiography (DiSE) and Perfusion Scintigraphy (DTS) in large cohorts of vascular patients.
Methods: Prior to major vascular surgery 2204 consecutive patients were screened for cardiac risk factors: age>70 years, history of myocardial infarction, angina pectoris, heart failure and diabetes mellitus. These patients then also underwent DiSE (n=394), DSE (n=1093), or DTS (n=717) testing. Positive DiSE or DSE results were defined as new or worsening wall motion abnormalities (NWMA), whereas a positive test result for DTS was defined as a reversible perfusion defect during stress. Logistic regression analyses were applied to evaluate the relation between clinical risk factors, noninvasive cardiac tests, and a composite of cardiac death or non-fatal myocardial infarction (MI).
Results: There were 138 patients (6.3%) with cardiac death or MI. Patients with 0, 1-2, and 3 or more clinical risk factors experienced respectively 3.0%, 5.7%, 17.4% cardiac events. No statistically significant difference was observed in the predictive value of NWMA for DiSE and DSE (Odds ratio (OR) 37.1 [95%CI, 8.1-170.1] vs. 9.6 [95%CI, 4.9-18.4]; P=0.12), whereas a positive test result for DTS had significantly lower prognostic value (OR=1.95 [95%CI, 1.2-3.2]). Estimated cardiac event rate for individual patients according to the number of risk factors and test result is shown in the table.

Estimated cardiac event rate

No. of Risk Factors	SE		DTS	
	negative	positive	negative	positive
0	1%	15%	4%	3%
1 to 2	1.3%	10.4%	11%	16%
>3	3.3%	27.6%	20%	31%

SE, stress echocardiography; DTS, dipyridamole perfusion scintigraphy

Conclusion: A result of stress echocardiography effectively stratified patients into low- and high-risk groups for cardiac complications, irrespective of clinical risk profile. In contrast, a positive DTS result did not differentiate between those who did and did not have a cardiac complication.

P3005 Cardiac death in scleroderma: a linkage with autonomic dysfunction

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Ventricular arrhythmias and cardiac death occur in patients with systemic sclerosis (SSc), even in absence of overt myocardial dysfunction- In order to evaluate the eventual prognostic significance of abnormalities in autonomic nervous control of the heart, or in ventricular repolarisation. as compared to other validated humoral and clinical markers of disease severity, 100 patients with systemic sclerosis (SSc) without overt myocardial involvement at Echo-Doppler examination, neither other systemic disease, underwent prospectively 24-hour ECG ambulatory recording while free-living spontaneous. A computerized algorithm was used to identify T wave on the precordial lead and to measure the QT interval; QTc was computed by the Bazett's formula; heart rate variability was investigated by means of time-domain and spectrum analysis. Out of the 100 SSc patients (17% males, 83% females, aged 54.8 ± 12.1 years, mean ± S.D., 64% was diagnosed with the limited form of the disease, 15% with the intermediate, 21% with the diffuse form). At the survival analysis a mean follow-up of 2100 days has been assessed, wit an overall mortality of 22% and cardiac mortality of 5%. Many conventional clinical and humoral markers of disease severity were considered with EKG-derived indices in the statistical analysis. Multiple logistic regression with forward stepwise selection (Wald) has been used to test the independent relation between the death and the covariates found to be significant at the univariate logistic regression. Kaplan-Meier life table estimates of spontaneously occurring event-free survival have been used to summarize the follow-up. Statistical significance has been taken as a p value of < 0.05.
At the multivariate analysis, cardiac death was predicted by abnormalities in lung diffusion properties (p= 0.011; 95%CI for Odds Ratio -OR- 0.837 0.978), LF/HF ratio (p= 0.05; OR= 0.00001-0.044), LF (low frequency power, normalised units, p= 0,0264; OR= 0.591-0.968), whereas overall mortality was predicted by SCL70 antibodies level (p=0.004; OR= 2.366-102.391) and by LF/HF ratio (p= 0. 014; OR= 0.00001-0.0006). QT and QTc value had not prognostic value. Increasing values of SCL70 antibodies significantly augmented the probability of cardiac death, which was decreased by increasing values of LF/HF and LF power. The latter abnormalities, detectable by a feasible, non-invasive diagnostic approach, indicate the presence of autonomic cardiac neuropathy in SSc patients and its prognostic value as for cardiac and overall mortality.

P3006 Lack of effect of warfarin in patients with diabetes mellitus after myocardial infarction

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Following results of subgroup analyses in a previous study we investigated whether diabetes mellitus (DM) might adversely modify the effect of warfarin in the Warfarin Aspirin Re-Infarction Study (WARIS II). The entry criterion of this study was clinically stabilized acute myocardial infarction. Patients (n=3630) who had no clear indication/contraindication for any of the study drugs were randomly allocated to one of three regimens: aspirin 160 mg/d, aspirin 75 mg/d and warfarin with a target INR of 2 to 2.5, or warfarin alone aiming for an INR of 2.8 to 4.2. The average follow-up period was four years. The primary endpoint of the parent study was the composite of death, nonfatal reinfarction and nonfatal thromboembolic stroke.
At baseline the prevalence of DM was 6.8% in the warfarin group, 8.7% in the combination group and 9% among those allocated to aspirin alone (n.s). Altogether there were 241 endpoints in the aspirin group, 203 in the warfarin group and 181 in the combination group.
Outcome was calculated in in terms of odds ratios. DM was an effect modifier for the association between endpoints and treatment. Statistically significant heterogeneity was found for nondiabetic subjects (OR 0.75, 95% CI 0.60-0.93) versus diabetic subjects (OR 1.54, 95% CI 0.80-2.94), p=0.038. The odds ratio exceeded 1 in diabetic patients, hence suggesting an adverse effect of warfarin therapy in this group. A Cox model was used to control for the effect of age and gender within the two strata. The following risk ratios (95% CI) and p-values were calculated for therapy with warfarin vs. aspirin (table):

	Warfarin + aspirin vs aspirin	Warfarin vs aspirin
Non-diabetes	0.65 (0.53-0.81) p=0.0001	0.79 (0.64-0.96) p=0.022
Diabetes	1.48 (0.88-2.50) p=0.14	1.52 (0.87-2.63) p=0.14

Our observation suggest a lack of a beneficial effect by warfarin therapy in subjects with diabetes mellitus, when the therapy is given for the sole purpose of prophylaxis after a sustained myocardial infarction.

P3007 Initiation of therapy with angiotensin-converting enzyme inhibitors in patients with severe angina pectoris and heart failure

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Background: One of the risk factor of first-dose hypotension (FDH) in pts with angina pectoris and heart failure (HF) is high doses of vasodilators and beta-blockers. Therefore, we investigated the first-dose effects of various angiotensin-converting enzyme inhibitors (ACEI) by monitoring 24-hour blood pressure (BP) in patients with severe angina pectoris and HF.
Methods: 85 male pts (mean age 56.0±1.0 years) with stable severe angina pectoris (CCS class III-IV) and HF (NYHA class II-III, mean 2.5±0.1, mean ejection fraction 32.1±0.6%) were included into the single-blind, parallel-group study. Mean BP (MBP), was calculated every 15 minutes during the first 24 hours of the study. First-dose hypotension (FDH) was defined as MBP fall >20 mm Hg. At the first stage 55 pts were randomized to captopril 6.25 mg, enalapril 2.5 mg, ramipril 1.25 mg, cilazapril 1.25 mg and perindopril 2 mg. Diuretic therapy was stopped 24 hours before ACEI initiation. At the second stage of study FDH of two ACEI with the least hypotensive effects (perindopril and enalapril) in 30 pts were investigated. Concomitant treatment with isosorbide dinitrate (41.9±2.8 mg/24h) and bisoprolol (10 mg/24h) was continued.
Results: Maximal reduction of MBP was -25.6±2.7% (captopril), -21.3±1.8% (enalapril), -24.5±3.6% (ramipril), -22.0±2.6% (cilazapril) and -16.1±2.8% (perindopril). In pts taking combined antianginal therapy first dose of enalapril produced maximal reduction of MAP on 20.4±1.9% while perindopril on 15.7±1.8% (p=0,05). MAP decrease on 20 mm Hg and more was 46.7% in enalapril group and 13.3% in perindopril group (p=0,03). Analysis of MAP hourly average changes showed BP reduction at 2H (-5.7 mm Hg, p=0.01), at H3 (-5.7 mm Hg, p=0.002) and H10 (-8 mm Hg, p=0.02) in enalapril group while in perindopril group there was no significant BP reduction. The attacks of angina were fixed at 20% pts only in enalapril group.
Conclusion: FDH is an important factor that might explain underuse of ACEI in patients with HF and angina pectoris. However, ACEI might differ in their safety profile at initiation of therapy. Large comparative trials are indicated.

P3008 Effects of a missed dose of antianginal therapy evaluated by 24-hr ambulatory electrocardiogram monitoring and exercise testing. Data from the CAPE II study

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Aim: In clinical practice, patients (pts.) frequently miss doses of antianginal medication. The aim of this study was to compare the consequences on myocardial ischemia of missed doses of different medical regimens.
Methods: 212 pts.(177 male, 25 female, aged 61±8 yrs) were included in a randomized trial comparing 2 drug regimens during stable dosing. Three-day ambulatory ECG monitoring (AECG) and exercise testing (ET) were performed on regular therapy with Amlodipine (A: 106 pts.), Diltiazem (D: 96 pts.) and combination therapy: A + Atenolol (AT;104 pts.) or D + 5 mononitrate (5mn; 91 pts.). On the third day of AECG pts. were given a matched placebo to simulate omission of a single drug dose, and both tests AECG and ET were repeated. The variables measured were for ET: time to 1mm ST depression (TimeST1), time to angina (TimeAng.), exercise duration (Ex.Dur), and for AECG: Nb ischemic episodes (N.epis.), total duration of ischemia (Isch. Dur.). Findings on active treatment were compared to those after omission. Statistics concern between treatments comparisons of changes due to omission.
Results:

Variables	Changes in	monotherapy		Changes in	combination	therapy
	A	D	p	A	D	p
ET						
Ex. Dur. (sec)	-2±63	-22±78	0.039	-14±67	-41±79	0.010
Time ST1 (sec)	0±97	-24±116	0.021	-17±85	-45±99	0.049
Time Ang. (sec)	-5±74	-6±89	0.847	-13±75	-45±85	0.005
AECG						
N. Epis. (/24h)	12	92	0.005	71	145	0.276
Isch. Dur. (min)	-215	800	0.022	1364	1498	0.696

Conclusions: Thus there are important clinically relevant differences in the impact of missed doses of different drug regimen, evaluated both by exercise test and by AECG. In contrast to (D) +5momonitrate, the intrinsically long acting calcium channel blocker (A) provides consistent benefits as monotherapy or in combination with atenolol.

P3009 Recurrent ischaemia in acute coronary syndromes: differential impact of electrocardiogram changes on outcomes

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It is generally accepted that reinfarction following myocardial infarction is associated with worse short- and long-term outcomes but few data are available regarding the various types of recurrent ischaemia (RI) and their impact on outcomes after acute coronary syndromes (ACS). The Global Registry of Acute Coronary Events (GRACE) is an international registry of patients with ACS in 94 hospitals and 14 countries. We analysed the demographics and outcomes of 17,511 patients with and without in-hospital RI (see Table for results).
Results: Multivariate analysis showed that male gender, history of previous angina, infarction, low heart rate, elevated systolic blood pressure and bleeding were independent predictors of RI during the hospital stay. Finally, RI itself was an independent predictor for hospital death after adjusting for baseline characteristics: the whole ACS population (odds ratio(OR): 1.6, 95% confidence interval: 1.36-1.95); and among patients presenting with ST-segment elevation myocardial infarction (STEMI) (OR: 1.96, 95% confidence interval 1.36-1.98), and non-STEMI/unstable angina (OR: 1.5, 95% confidence interval: 1.17-1.99).
Conclusions: RI is a frequent event in patients admitted with ACS (30.2%) but its impact is highly dependent on electrocardiographic (ECG) changes or reinfarction. Two-thirds of patients with RI have neither reinfarction nor ST changes and their outcomes appear to be very similar to those of patients without RI. Conversely, in ACS patients with reinfarction or with RI and ST changes (9.7% of all ACS pts), in-hospital outcomes were worse and length of stay was longer. These results highlight the persistent need for improvement in the treatment of ACS.

P3010 Long-term cardiac medication after acute myocardial infarction: is it maintained consequently?

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Long-term therapy with aspirin (ASS), beta-blockers (BB), lipid lowering drugs (LLD) and ACE inhibitors (ACE) improves short and long-term prognosis of patients (pts) suffered from acute myocardial infarction (AMI). However, little is known about wether medication at hospital discharge is maintained during subsequent follow up. Between May 1999 and December 2000, 400 consecutive pts with AMI (72% male, mean age 61 years) were included in the Berlin Myocardial Infarction Study. Cardiac medication was documented at hospital discharge. Follow up was performed after 6 and 12 months (mean 259 and 449 days) with documentation of the actual medication. Information was obtained with a standardized questionaire by telephone contact and clinical visit.
Results: Among the 400 pts discharged from hospital after AMI, follow up response was 97% (388). 12 months follow up mortality was 10% (40/388).
There was no significant drop-out rate in taking ASS during follow up: among all 348 survivors 87% (303/348) received ASS at discharge, 6 months later 89% (306/348) and 12 months later 86% (301/348). The respective numbers for BB are 93% (324/348) vs. 82% (286/348) vs. 80% (278/348) (p=0,0001 for the comparison discharge vs. 6 months, p=0,0001 for the comparison discharge vs. 12 months), for LLD 81% (282/348) vs. 70% (243/348) vs. 67% (233/348) (p=0,0006 and p=0,0001) and for ACE 54% (188/348) vs. 51% (178/348) vs. 57% (198/348)(for both n.s.).
Conclusion: The present results indicate that pts behavior in taking ASS and ACE remains constant during one year follow up. Nonetheless there is a substantial drop-out-rate of benificial long-term medication with BB and LLD. Wether this is due to inadequate patient education, decreasing budget or limited patient compliance due to side-effects, has to be investigated.

P3011 Do we have to treat asymptomatic patients after myocardial infarction with angiotensin-converting enzyme inhibitors and betablockers? Results from the ABC-trial

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Introduction: Combined treatment with ACE-inhibitors and betablockers of symptomatic patients suffering from heart failure (NYHA II-IV) is well established. Until now there was no randomized, controlled study for asymptomatic patients with only moderate reduced left ventricular ejection fraction (LVEF >40%) after myocardial infarction (MI) available.
Methods: 160 asymptomatic patients (mean age 59 years, 135 male, 25 female) after MI with a LVEF >40% were treated for 18 month with open label (OL) Metoprolol (Meto) or Ramipril (Rami). In addition patients were randomized to receive a double-blinded (DB) medication with either Placebo (Pla) or the corresponding medication (Meto or Rami). This resulted in 4 patient groups: group (G) 1: Meto (OL) + Rami (DB); G2: Meto (OL) + Pla (DB); G3: Rami (OL) + Meto (DB); G4: Rami (OL) + Plac (DB). Primary endpoint was LVEF after 18 months. There was no difference in the baseline LVEF between the 4 groups.
Results: LVEF after 18 months in G1 was 48,6% (±13,1), in G2 46,2% (±13,4), in G3 48,8% (±10,7) and in G4 50,8% (±9,9%) (p=ns).
Conclusion: The combination of ACE-inibitors and Betablockers compared to monotherapy with either one in asymptomatic patients with only moderate reduced LVEF after MI did not result in a higher LVEF after 18 months. Further studies are warranted to clerify the value of combined treatment compared to monotherapy in this patient group.

Abstract P3009 – Table: Outcomes with and without in-hospital RI

	RI	Reinfarction	RI with ST-seg changes	RI without ST change or reinfarction	P comparisons for the three types of RI	Without RI	P (with vs without RI)
N (%)	4828 (30.2)	261	1433	3134		11,170 (69.8)	
Age (years)	66.7	69.0	67.5	66.0	<0.0001	66.0	NS
Male (%)	64.0	64.3	63.4	63.6	0.9623	68.4	<0.0001
STEMI at admission (%)	35.8	67.4	41.0	30.8	<0.0001	44.4	<0.0001
Death (%)	5.6	29.5	7.2	3.0	<0.0001	5.0	0.022
Congestive heart failure (%)	16.6	34.8	19.7	13.7	<0.0001	13.8	<0.0001
Cardiac arrest (%)	5.7	27.1	8.0	3.0	<0.0001	4.8	0.018
Median length of stay (days)	7	12	8	7	<0.0001	6	<0.0001

Demographics and outcomes of 17,511 patients.NS=not significant

P3012 Concerted action of various angiogenic factors during acute myocardial infarction in patients: the three lines of defense

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It is well documented that angiogenesis plays a key role in the process of ventricular remodeling following acute myocardial infarction (AMI). However, the exact contribution of each of the numerous angiogenic agents in this process is still an issue of debate. We sought to evaluate the role of three major angiogenic peptides: free Insulin-like Growth Factor-1 (fIGF-1), basic Fibroblast Growth Factor (bFGF) and Angiogenin (ANG), in AMI patients.

Methods: 40 pts with first attack of AMI admitted in our department and thrombolysed during the acute phase,without previous history of any other disease, were examined for plasma levels of fIGF-1, bFGF and ANG, measured by ELISA, and compared to corresponding levels of 20 sex and age- matched normal controls (NC) with mean values: 7,78 ± 0,75 ng/ml for fIGF-1, 1,62 ± 0,53 pg/ml for bFGF and 210,12 ± 25,6 ng/ml for ANG. Plasma samples were collected on hospital admission (0 hours) and 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 3 days, 4d, 5d, 7d, 15d and 30d thereafter.

Results: Data is expressed as mean values ± SEM in ng/ml for fIGF-1 and ANG and in pg/ml for bFGF. For the statistical analysis the non-parametric Wilcoxon test was used with a statistical significance of $p<0,05$ compared to corresponding values of: a) NC (*), b) the relevant plasma value on admission (°). fIGF-1 exhibited significantly high initial plasma levels on admission (10,92 ± 0,93 *) followed by a gradual increase up to a maximum level at 36h (16,64 ± 2,12 *°). This peak was succeeded by a progressive decline that ended to a minimum value at 30d (12,14 ± 1,35 *). bFGF developed a significant early peak at 0h (5,27 ± 1,13 *) followed by a steep decline leading to a nadir at 24h (1,63 ± 0,46 °), that was reversed leading to a late peak at 15d (8,93 ± 2,06 *). ANG also exhibited a double-peak increase at 0h (327,12 ± 31,75 *) as well as at 4d (305,86 ± 29,44 *) with the lowest plasma value at 24h (233,74 ± 18,32 °).

Conclusions: Thus, the activation of the numerous angiogenic agents seems to be triggered at different time points. Some of them exhibit an immediate peak shortly after AMI onset probably as a result of acute hypoxia due to coronary artery occlusion, while others develop an intermediate or a late peak, therefore exerting their cardioprotective potential in three distinct lines of defense. At the same time, they all act in concert to stimulate angiogenesis either by playing a pivotal role in the induction of this process, or by manipulating its multiple steps later in an attempt to modulate ventricular remodeling and preserve cardiac function.

P3013 Changes in the frequency spectrum of the endocardial electrogram in acute myocardial ischaemia and recent infarction

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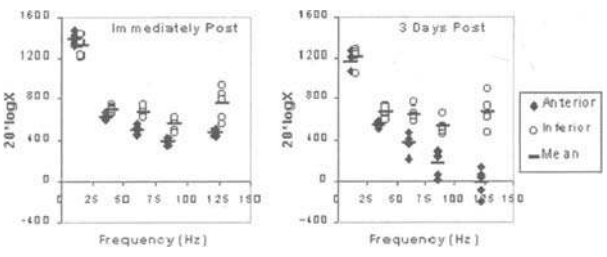
Peak-to-peak unipolar endocardial voltage (Vuni) is useful in identifying chronically infarcted myocardium but is insensitive in recognising acute ischemia. Vuni also has limited spatial resolution, due to significant far-field effects. We postulated that analysis of the high frequency components of the electrogram would improve the delineation of acute and chronic ischemia.

Methods: Eight dogs underwent LAD ligation and had 'Biosense' electromechanical mapping and echocardiography performed at baseline and immediately post-occlusion. Five dogs survived to repeat the studies at 3 days. A representative electrogram was obtained for the ischemic anterior zone and the remote inferior zone for each ventricle. Frequency spectra for each zone were obtained by performing FFT and a log scale was used to amplify high frequency components.

Results: Small baseline differences were found; anterior zones having a larger low frequency (0-30 Hz) component (p=0.02) and inferior zones a larger high frequency (>50 Hz) component ($p<0.03$). Immediately post-occlusion, there was a small reduction in voltage throughout the spectrum in both zones, while a consistent more prominent reduction occurred in the high frequency components (>30 Hz) of the anterior zones ($p<0.005$). At 3 days, a further diffuse reduction was noted in amplitude, but predominantly in the very high frequency components (>75 Hz) of the anterior zones ($p<0.02$). A clear threshold could distinguish between the high but not the low frequency components of ischemic and remote zones in all ventricles in acute ischemia (p=0.0005) and in recent infarction (p=0.002).

Thus, specific changes in the frequency spectrum of the endocardial electrogram permit a consistent distinction between ischemic and remote zones.



Frequency spectrum.

P3014 Differences in hospital reinfarctions complicating acute myocardial infarction as observed in current randomised trials will not influence long-term mortality

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Background: In 2001 three large RCT's (GUSTO V, ASSENT 3, HERO 2) on non-mechanical reperfusion strategies in AMI were published. All studies did not find a mortality benefit for the new treatment strategies, however they found a reduction in the rate of non-fatal hospital reinfarction from 1.1% to 2.4%. Non-fatal in-hospital reinfarction is known to be a predictor of further death. Therefore the true benefit of the new treatment strategies might be realized at late follow up.

Methods: We analysed the prospective observational MITRA data base selecting AMI patients similar to the RCT patients, to determine whether the observed differences in reinfarction rates will have a influence on long term mortality.

Results: Out of 6737 patients included in MITRA between 1994 and 2000 and a completed follow-up, 2109 (31%) fulfilled the selection criteria. Non-fatal in-hospital reinfarction occurred in 3.6% of patients. During the hospital stay urgent coronary revascularization (PCI or CABG) was performed in 43.4% of patients with non-fatal reinfarction compared to 12.5% without non-fatal reinfarction ($p<0.001$). Follow-up was performed at a median of 18 months.

Mortality at 1-year after discharge was 6.8% (95%CI: 2.3% - 11.3%) in patients with versus 4.4% (95%CI: 3.5% - 5.3%) in patients without a non-fatal reinfarction (absolute difference 2.4%, p = 0.04 by log rank test). Using the largest difference in non-fatal reinfarction rates described by the RCT's of 2.4% (ASSENT 3 trial) case load calculation resulted in 4111792 patients needed to find a significant difference in 1-year mortality. Even in the "worst" scenario, using the upper and lower 95%CI limits, still 317748 patients would be needed.

Conclusion: Our data make it very improbable that the observed differences in the rates of non-fatal in-hospital reinfarctions between the treatment arms in the GUSTO V, the ASSENT 3 and the HERO 2 trials will result in reduced 1-year mortality rates.

P3015 New heart rate variability algorithm is a powerful tool for risk prediction after acute myocardial infarction

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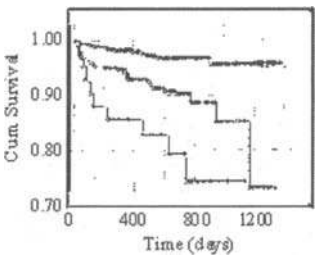
Aim of the study: To validate a new HRV algorithm in post MI patients derived from 24 hour Holter recordings.
Methods: The algorithm selects all RR intervals in 24-hour Holter ECGs which are slightly longer (>100% & <=105%) than their preceding RR intervals and calculates the mean interval prolongation (MIP).
The cut-points of MIP were optimised in a training sample consisting out of 591 patients (primary endpoint: total mortality, median follow up 22 months). The method was validated in the ATRAMI population (1284 patients, primary endpoint: fatal or non fatal cardiac arrest, median follow up 20 months). Univariate and multivariate analyses (sex, age, HRV index, SDNN, mean heart rate, LVEF, baroreflex sensitivity (BRS)) were performed.
Results: In the training sample, we observed two optimal cut-points for MIP: 8 ms and 18 ms. In the ATRAMI population, LVEF was the strongest univariate and MIP the second strongest risk predictor (p=0,0037 and p=0,0038, respectively). With multivariate analysis, LVEF, MIP and BRS were independent risk predictors (LVEF: p=0,0061; MIP: p=0,0017; BRS: p=0,021). Kaplan Meier survival curves of patients with MIP >= 18ms, 8-18ms and <8ms are shown in the figure.



Conclusions: MIP is a strong and independent risk predictor in post-infarction patients.

ENDOTHELIAL FUNCTION

P3016 Endothelial dependent vasodilatation and incidence of cerebrovascular events in healthy postmenopausal women

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Background: Postmenopausal women have been shown to have abnormal endothelium-dependent vasodilatation (EDVD). However, the prognostic role of an impaired EDVD was only poorly investigated, particularly in relation with the incidence of cerebrovascular events (CE). This study was aimed to investigate the relationship between an abnormal EDVD and the long-term incidence of CE. It also allowed the assessment of CE risk in a less studied specific subgroup of patients.
Method: 188 consecutive healthy postmenopausal women (mean age 65 ± 11 years) underwent a ultrasonographic study of the brachial artery, and were then followed up for a mean period of 75 months (range: 67-88). Women with previous cardio and cerebrovascular diseases, hypertension, diabetes mellitus, hyperlipidemia were excluded from the study. EDVD was evaluated by measuring the diameter of the brachial artery before and during reactive hyperaemia (induced after deflation of a blood pressure cuff inflated to suprasystolic pressure for 5 minutes) and was calculated from the diameters as: (reactive hyperemia – baseline)/baseline X 100%.
Results: The median value of EDVD in the entire study population resulted in 9.5% (25th-75th percentiles were 6.4% and 12.9%, respectively). The 94 women with an EDVD < 9.5% were classified in group 1 (abnormal EDVD); the remainder women (n = 94), with an EDVD > 9.5%, in group 2 (normal EDVD). There were no intergroup differences regarding age, blood pressure values, cholesterol plasma levels, fasting glucose plasma levels, duration of menopause and hormone replacement therapy use. During follow up, 14 of 94 women (14.9%) experienced a CE in group 1 (abnormal EDVD), versus 4 of 94 (4.2%) in group 2 (normal EDVD) (p < 0.0001). There were 12 cases of transient ischemic attack (TIA) in group 1 as opposed to 3 cases in group 2 (p < 0.0001). Moreover, only few women experienced an ischemic stroke (2 cases in group 1 versus 1 case in group 2; p = ns). Multivariate logistic analysis revealed that an abnormal EDVD [Odds Ratio = 2.89 (95% Confidence Intervals from 1.76 to 4.43)] is the only variable that remainder as a significant and independent predictor of TIA in our population. All the cases were validated by review of hospital records.
Conclusions: This study demonstrates that an abnormal EDVD clearly identifies postmenopausal women with an high risk of TIA.

P3017 The plasma NO/ET-1 ratio is a useful marker for the grade of coronary vascular disease

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Background: The arterial endothelial function (AEF) is used for detecting of coronary vascular disease (CVD) in clinical research setting. Further it is regulated by local release of nitric oxide (NO) and endothelin-1 (ET-1). However there were no reports whether AEF and/or plasma NO/ET-1 ratio can be useful marker in comparing with exercise testing (EXT) and coronary risk factors. Methods: We measured the brachial artery (BA) vasodilative response to both endothelium-dependent (ED) and endothelium-independent vasodilation (EID, NTG 0.3mg SL) by using high resolution ultrasounds(7.5MHz) of 38 hypertensive patients (HT pts) with normal coronary artery and 32 patients with CVD (>=70%). The plasma NO and ET-1 levels were measured using ENO-200 and RIA. Soon after these procedures, symptom limited EXT was performed by Bruce protocol. Results:The sensitivity and specificity for detecting of CVD in plasma NO/ET-1 ratio >= 2.0 was 90% and 85%, whereas ST depression >=1.0mm (80 msec from J point) was 80% and 78%.

	BA-RH (%)	BA-IND	NO/ET-1	ST	TC	HDL
CVD	5±6	6±7	1.1±1.1	-1.4±0.9*	199±36	52±36
HT	6.3±4	10±4*	2.7±2.2**	-0.8±0.4	189±36	51±16

Conclusion: Our results suggest that plasma NO/ET-1 ratio is a useful new marker for estimating of CVD, which is equivalent to usual EXT and superior to AEF. EXT capacity might be based on vasodilative and vasoconstrictive products ffrom AE cell. (*p<0.05 **p<0.01)table

P3018 Chronic smoking is associated with endothelial dysfunction and increased levels of tumour necrosis factor-α, interleukin-1β and interleukin-6

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Background: Smoking is known to be associated with endothelial dysfunction, mainly through an increase of oxidative stress. Tumor necrosis factor (TNF-a), a pro-inflammatory cytokine as well as interleukines -1b (IL-1b) and -6 (IL-6) are implicated in the pathogenesis of atherosclerosis. In this study we investigated the effects of chronic smoking on endothelial function, inflammation and lipid peroxidation.
Methods: In this study, 45 smokers (23 males 22 females, aged 34±1 years, smoked 18.1±2.1 pack-years) and 11 non smokers (6 males 5 females, aged 30±2years) were enrolled. Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to post reactive hyperemia blood flow. Endothelium independent flow (NTR%) was assessed as the % change from baseline to post sublingual nitroglycerin administration flow. Serum levels of TNF-a, IL-1b and IL-6 were determined by enzyme linked immunosorbent assay. Lipid peroxidation was evaluated by measuring lipid hydroperoxides (LPO) using a spectrophotometric assay. All values are expressed as mean±SEM.
Results: Blood pressure, heart rate, body weight, basal forearm blood flow and NITR% were similar between smokers and non smokers. FMD was significantly greater in non smokers (111.2±17.1%) compared to smokers (49.8%±3.0, p<0.001). Plasma levels of TNF-a, IL-1b and IL-6 were significantly greater in smokers (1.73±0.12, 0.21±0.022 and 2.55±0.46, pg/ml respectively) than in non smokers (1.1±0.10, 0.12±0.011 and 0.80±0.12 pg/ml respectively) (p<0.05 for TNF-a and p<0.01 for interleukines 1b and 6). However plasma level of LPO was not significantly different between the two groups. Pack-years was correlated with FMD (r=-0.475, p=0.001) and serum levels of TNF-a (r=0.379, p=0.004), IL-1b (r=0.227, p=0.048) and IL-6 (r=0.438, p=0.002).
Conclusion: Smoking is associated with endothelial dysfunction and increased levels of TNF-a, IL-1b and IL-6. These findings provide evidence that smoking may be associated with a vascular inflammatory process.

P3019 Impaired endothelial function and increased intina-media thickness of the common carotid arterial wall in patients with â-thalassemia major

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Cardiovascular complications are common in patients (pts) with b-thalassemia major (bTM). Both endothelial dysfunction and thickening of the carotid arterial wall are associated with atherosclerosis or its risk factors. In pts with bTM an increased vascular oxidative stress has been reported. Desferrioxamine has favorable effects on endothelial dysfunction in pts without bTM.

Methods: We evaluated endothelial function and thickness of the common carotid arterial wall in pts with bTM by means of high-resolution ultrasonography. In twenty seven pts with bTM (age 25±7years, serum ferritin 2380±1664 ng.ml-1, 59% on optimal chelation therapy) without cardiac disease or diabetes mellitus and 27 healthy control subjects, flow-mediated dilatation (FMD) was measured as % change of the post-ischemic right brachial artery (BA) diameter. Endothelium-independent, nitroglycerin-induced vasodilatation (NID) and intima-media thickness (IMT) of the posterior common carotid arterial wall were also assessed.

Results: (table 1) The two groups were matched for age, gender, body surface area, blood pressure and smoking habits. Serum cholesterol was lower in pts with bTM (124±37 versus 185+33 mg.dl-1, $p < 0.0001$).

(table 1)

	Patients with bTM	Healthy subjects	p
BA diameter (mm)	3.84±0.66	3.95±0.58	ns
Post-ischemic BA blood flow (ml.min-1)	341±209	384±174	ns
FMD (%)	6.98±2.5	10.05±4.2	<0.01
NID (%)	14.86±6.22	16.66±4.23	ns
Carotid artery IMT (mm)	0.51±0.08	0.45±0.06	<0.01

No correlation was found between FMD or IMT and serum ferritin levels. Conclusion: These data point toward a proatherogenic milieu with reduced bioavailability of nitric oxide in thalassemic patients despite near absence of cardiovascular risk factors. Our findings may be explained by iron-mediated oxidative stress on vascular endothelium.

P3020 The effect of red wine on endothelial function and oxidative stress in patients with acute coronary syndrome

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Background: Moderate red wine consumption may improve endothelial function in normal volunteers. This can be related with antioxidant properties present in red wine. Since in coronary patients both endothelial dysfunction and oxidative damage play an important role, we sought to explore the effects of moderate red wine consumption on these parameters in patients with an acute coronary syndrome (ACS).

Methods: We enrolled 20 patients treated with PTCA and stent after an acute coronary event (unstable angina and non Q AMI). All patients received treatment with step 2 AHA diet, aspirin, clopidogrel, betablockers and atorvastatin. Patients were randomly selected to a red-wine group (n= 9, 250 ml daily, Cabernet Sauvignon variety) or to a control group (n= 11, abstinence from alcoholic beverages). Studies were performed at baseline and after 2 months. Endothelial function was estimated by flow mediated vasodilatation of the brachial artery using a 3-11 mHz linear array transducer at 1, 2 and 3 min after releasing the cuff pressure. To evaluate plasma antioxidant capacity, we measure total antioxidant reactivity (TAR) using a free radical generator and chemiluminiscence, and ferric reducing antioxidant power (FRAP). Oxidative damage was evaluated by 8-OH deoxyguanosine measurements (8-OHdG). Data are shown as mean ± standard error and differences were compared by paired or unpaired t test as appropriate.

Results: There were no diferences in clinical outcomes at follow-up. Flow mediated vascular reactivity increased by 37% (P= 0.20) and 109%($P<0.01$) in control and wine groups, respectively. Total Cholesterol/HDL ratio was significantly increased by approximately 21% in both groups ($p< 0.04$). Plasma total antioxidant capacity increased significantly only in the wine group, from 273±20 to 330±15 μM for TAR ($P<0.03$) and 1219±82 to 1449±63 μM for FRAP ($P<0.001$). Oxidative DNA damage in controls decreased from 13.1±1.1 to 10.0±1.0 ($P<0.003$) whereas with wine, it decreased from 13±0.8 to 5.6±0.7 per 100000 guanosines ($P<0.001$; p=0.002 vs control).

Conclusion: Conventional therapy after an ACS managed with PTCA was useful to reduce lipid alterations and decrease DNA damage, whereas it did not increased significantly brachial reactivity. The addition of moderate red wine consumption to conventional therapy increased plasma antioxidant capacity and decreased DNA damage, which may be related with a significant improvement in endothelial function.

P3021 Endothelial function in salt-sensitive healthy subjects with parental hypertension: strategies of pharmacological correction

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Endothelial dysfunction has been considered as a main factor in the development of salt-sensitive hypertension. Previously we have showed that ACE inhibitors significantly improved endothelial function in patients with salt-sensitive essential hypertension. The aim of our study was evaluation of endothelial function in salt-sensitive healthy offspring of hypertensive patients.

Methods: A total of 22 healthy salt-sensitive subjects (12 males, 10 females aged 19 to 26 years) with well documented history of parental hypertension were studied. Age matched control group included 18 healthy subjects whose parents did not suffer from essential hypertension. Salt sensitivity was determined by Weir (1986) method. NO was directly measured by electron spin resonance spectroscopy. Plasma big endothelin (ET-1) level was determined by extraction-based competitive radioimmunoassay (Biomedica; Vienna, Austria).

Results: NO production was reduced approximately by 27% in salt-sensitive subjects in comparison with the control group. In contrast plasma levels of Big ET-1 were significantly increased in offspring of hypertensive patients (8.8±0.87 pmol/l vs. 4.6±0.55 pmol/l in controls, $p<0.05$). Administration of lisinopril resulted in increase of NO production and reduced Big ET-1 plasma levels in salt-sensitive healthy subjects.

Conclusion: Endothelial dysfunction has been revealed in healthy salt-sensitive subjects with parental hypertension, which might be the main mechanism of predisposition to essential hypertension. Early treatment of salt-sensitive healthy subjects with ACE inhibitors is considered to be a valuable method of primary prevention of essential hypertension.

P3022 Endothelial function is negatively correlated to ST-segment depression during exercise in women with angina and normal coronary arteries

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Background: Women with chest pain and normal coronary arteries present a common and often difficult clinical scenario. It has been suggested that some may have myocardial ischaemia, caused by microvascular disease and that endothelial dysfunction with reduced vasodilator capacity might be an aetiological factor. It is often difficult to separate those with microvascular angina, from those with a non-cardiac aetiology of their chest pain.

Methods: We recruited 51 women with both an electrically positive exercise tolerance test (ETT) and a coronary angiogram in the previous two years demonstrating normal epicardial vessels. The ETT was repeated with manual measurement of maximal ST segment deviation. Endothelial function (EF) was assessed non-invasively in the forearm cutaneous vascular bed by means of laser-doppler imaging in response to iontophoretic application of acetylcholine (ACh) and sodium nitroprusside. An arbitrary cut-off point of 10000 units (area under the curve) for the ACh response was used to categorise subjects those with 'normal' or 'impaired' EF.

Results: 33 women (65%) had impaired EF. Only 13 women (26%) had a second unequivocally positive ETT (greater then 2mm ST depression). There was a negative linear correlation between the extent of ST depression and EF ($r=0.44$ $p=0.001$). All 13 women with greater than 2mm ST depression had impaired EF and no women with 'normal' EF had 2mm or more of ST depression. However, 20 women with 'impaired' EF did not have significant ST depression. In addition, 25 healthy aged-matched controls were recruited and had their endothelial function measured. There were statistically significant differences between the EF of the controls and that of the 13 women with a positive ETT Discussion. There was an association between endothelial dysfunction and ST changes on ETT in these women with chest pain and normal coronary arteries. Women with reproducible ECG changes had impaired EF when compared to healthy controls. Our data suggest a potential novel application of non-invasive assessment of endothelial function as an adjunct to ETT in identifying with greater sensitivity and specificity, women with and without microvascular angina. This hypothesis should be tested in an independent sample of these patients.

P3023 Reactive hyperemia peripheral arterial tonometry: a novel non-invasive test to identify patients with coronary endothelial dysfunction

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Background: Coronary endothelial dysfunction (CED) is considered the very early stage of coronary atherosclerosis and is associated with myocardial ischemia and an adverse prognosis. Because CED is reversible early identification of this disorder may have therapeutic implications. Reactive hyperemia peripheral arterial tonometry (RH-PAT) is a novel, non-invasive plethysmographic method to assess peripheral vasomotor function using a finger-mounted probe. This study was designed to test the hypothesis that CED is associated with an attenuation of RH-PAT values.

Methods and Results: 31 patients without obstructive coronary artery disease, undergoing coronary endothelial function testing with graded intracoronary acetylcholine infusion, were studied and divided into two groups according to the presence (n=15) or absence (n=16) of CED. Using RH-PAT digital pulsatile arterial volume changes were assessed at rest and during reactive hyperemia following transient complete brachial arterial occlusion with a blood pressure cuff. In addition, PAT response to the endothelium-independent vasodilator nitrogycerin was assessed in 8 patients with and 10 patients without CED. RH-PAT index was calculated as the ratio of the peak pulsatile blood volume response at 1, 2, 3, and 4 minutes after cuff deflation divided by the pulsatile blood volume changes at rest. RH-PAT indices were significantly lower in patients with CED compared to those with normal coronary endothelial function during the first 3 minutes of reactive hyperemia (1 minute: 1.3±0.1 vs. 1.8±0.1, p=0.002; 2 minutes: 1.3±0.1 vs. 1.6±0.1, p=0.006; 3 minutes: 1.2±0.1 vs. 1.4±0.1, p=0.04), whereas the PAT response to nitroglycerin was similar in both groups.

Conclusions: This study demonstrates that peripheral hyperemic response, as measured by RH-PAT, is attenuated in patients with CED, suggesting a role for RH-PAT as a novel, non-invasive test for the identification of patients with CED.

P3024 C reactive protein protects endothelial nitric oxide synthase expression in bovine endothelial cells in culture

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C reactive protein is a acute phase inflammatory marker and it has been considered as a coronary syndrome marker. However, C reactive protein can also produce biological actions.

Objective: The aim of our study was to analyze the C reactive protein effects on endothelial nitric oxide synthase expression (eNOS) in aortic bovine endothelial cells (BAEC) in culture.

Method and Results: BAEC were incubated with two different cytokines, tumor necrosis factor-alpha (TNF-alpha, 500 U/mL) or with interleukin-6 (IL-6, 10 ng/mL) during 24 hours in the presence and in the absence of increasing concentrations of C reactive protein (0-25 μg/mL). TNF-alpha reduced eNOS protein expression in BAEC and this effect was associated to an increase in the interaction of a 60 KDa cytosolic protein with the eNOS mRNA. This protein has been termed as endothelial dysfunction inductor protein (EDIP). C reactive protein protected eNOS protein expression in a dose dependent manner and reduced the interaction of EDIP with the eNOS mRNA. This effect was associated with a more prolonged half life of eNOS mRNA. Similar results were obtained with the IL-6. IL-6 reduced eNOS expression increasing the ability of EDIP protein to interact with eNOS mRNA. These effects were reverted in the presence of C reactive protein.

Conclusion: C reactive protein although it is considered as an inflammatory marker, protects eNOS expression reducing the interaction of EDIP to eNOS mRNA and favouring eNOS mRNA stability.

P3025 Endothelial function is associated with plasma levels of C-reactive protein in patients with coronary artery disease

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Endothelial function is impaired in patients with coronary artery disease (CAD), in these patients plasma levels of C-Reactive protein (CRP) are related to future cardiac events. Aim of the present study was to assess the relation between endothelial function and CRP in 73 patients (52 men, 21 women, mean age 66±9 yrs) with CAD. Endothelial function was evaluated by means of flow-mediated dilatation (FMD) of brachial artery following ischemia and CRP by means of a high sensitive assay. Baseline values of CRP and FMD were compared with those of 32 healthy controls (25 men, 7 women, mean age 65±11 years). After baseline evaluation patients underwent full medical therapy for 3 months at the end of which they were tested for endothelial function and CRP again.

Compared to healthy controls pts had significantly impaired endothelial function (FMD 3.6±3.2% vs 8±2.4%, $p<0.01$) and higher plasma levels of CRP (1.6±0.9 mg/dl vs 0.9±0.56 mg/dl, $p<0.05$). A significant negative correlation was found between plasma levels of CRP and FMD in patients with CAD at baseline ($r= -0.56$, $p<0.05$) while no correlation was found in controls. Medical therapy resulted in a significant improvement in endothelial function (3.64±3% vs 7.2± 3.5%, $p<0.01$), and a decrease of CRP (-0.26±0.19, $p<0.01$), the change in CRP and FMD was indepentent from the drug used. A positive correlation was found between improvement in FMD and degree of CRP reduction ($r= 0.57$, $p<0.01$).

In conclusion plasma levels of CRP are associated with and impaired endothelial function in patients with CAD suggesting a correlation between inflammation and integrity of the endothelium. Full medical therapy reduces CRP and parallely improves endothelial function.

P3026 Endothelial dysfunction is a feature of treated major depression

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There is increasing evidence that depression is a risk factor for the subsequent development of coronary heart disease (CHD), conferring an approximately twofold increased risk. Traditional risk factors for CHD (e.g. smoking, hypertension, diabetes and hypercholesterolaemia), are characterised by arterial endothelial dysfunction, which promotes atherogenesis and is a strong prognostic factor for CHD events. Arterial endothelial dysfunction has been reported in newly diagnosed, untreated depression and is a possible mechanism by which depression confers increased cardiovascular risk. It is not known if endothelial dysfunction persists after effective treatment of depression and symptom remission.

We studied 12 subjects (mean age 39, range 24 to 51, 6 male) who were being treated for primary major depression (DSM-IV criteria) and were in symptom remission, and 10 controls (mean age 37, range 24 to 55, 7 male). All subjects and controls were without other risk factors for CHD. Arterial endothelial function was assessed by measurement of brachial artery flow-mediated dilatation (FMD). We also measured baroreflex sensitivity (BRS), a measure of autonomic control of heart rate in response to changes in blood pressure. Arterial endothelial function measured by FMD was significantly impaired in the depression group(-0.7%, standard error of mean (SEM) 1.7%) compared to the control group (5.9%, SEM 0.9%) ($p=0.004$ by non-paired t-test) whereas glyceryl trinitrate-induced endothelium-independent dilatation of the brachial artery was similar in patients and controls (18.5% (2.4) v 19.0% (2.5), p=NS). BRS did not differ significantly between the groups.

In conclusion, arterial endothelial dysfunction, which has been demonstrated in newly diagnosed, untreated depression, is also present in treated depression. This abnormality may contribute to the increased risk of CHD and does not appear to improve with antidepressant treatment.

P3027 Heavy metal ions and function of vascular endothelium in patients with coronary artery disease

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There is well-established link between dysfunction of vascular endothelium and pathogenesis and progression of atherosclerosis. Many different factors can deteriorate or improve function of endothelium. Many other are still expected to be discovered. Among them we can list heavy metal ions (HMI): selenium (Se), zinc (Zn), lead (Pb), cadmium (Cd), manganese (Mn) and copper (Cu).
The aim of the study was to investigate the relation of concentration of Pb and Cd in blood and Se, Zn, Cu and Mn in plasma with function of endothelium in population of patients with coronary heart disease (CAD).
Study population consisted of 60 patients (32 men and 28 women) mean age 62,4 ± 10,5 yrs, all former or current smokers with no history of working in environment with high exposure to HMI. The diagnosis of coronary artery disease was established upon coronary angiography in which 70% narrowing of the vessel was considered as significant. Blood concentrations of Cd and Pb and plasma concentrations of Cu, Zn, Mn, Se were estimated by SAA method (Spectrophotometry Atomic Absorption). Plasma nitric oxide (NO) served as a marker of endothelial functional status and its level was estimated by ELISA method.
Results: In multivariate analysis significant partial correlations of NO with Zn ($r=0.4$, $p<0.004$), Mn ($r=0.9$, $p<0.002$) and Se ($r=0.76$, $p<0.02$) were revealed. Blood concentrations of Cd and Pb were below threshold limit value for non-exposed population and plasma concentrations of Zn, Mn, Se, Cu were within normal limits.
Conclusions 1. Se, Zn and Mn may have in normal concentrations positive effect on vascular endothelium expressed as production of NO in patients with CAD.

P3028 Direct biochemical evidence for enos stimulation by bradykinin in the human forearm vasculature

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Objective: Although it has been shown recently that acetylcholine (ACh)-induced vasodilation of forearm resistance vessels is almost entirely mediated by nitric oxide, direct biochemical evidence for eNOS stimulation by bradykinin (BK) in the human arterial circulation is still lacking. Therefore, the present study was designed to test the hypothesis, that in the human forearm vasculature eNOS stimulation significantly contributes to BK-induced vasodilation.
Methods: BK was infused in the presence and absence of the NOS inhibitor, L-NMMA (8 μmol/min) into the brachial artery of 16 healthy volunteers and the effects compared to muscarinergic NOS stimulation following acetycholine infusion. Forearm blood flow (FBF) was measured by venous occlusion plethysmography and plasma nitrite (NO2-), which represents a sensitive and specific marker of regional eNOS activity, was determined in the antecubital vein and brachial artery by flow injection analysis. Nitric oxide release was calculated as product of the veno-arterial difference of NO2- concentration times FBF. Results: Kininergic (BK: 20, 60, 200 ng/min) as well as muscarinergic (ACh: 1, 3, 10 μg/min) stimulation resulted in a dose dependent increase in FBF and NO2- in each individual. The relationship between FBF and NO release upon BK infusion was comparable to that obtained with ACh ($r= 0.98$; $n=96$, $p<0.01$). Moreover, eNOS inhibition reduced both flow responses and NO release (BK: 54 and 75%; ACh: 57 and 72%) to a similar extent. Conclusions: This is the first direct biochemical evidence for the involvement of eNOS in BK-induced vasodilation of human forearm resistance vessels. BK may represent a suitable alternative tool to assess disturbances of the L-arginine-NO-pathway in vivo.

P3029 Differential effects of nitric oxide species on human platelet function: interaction with thiols

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Background: Endothelial-derived relaxing factor (EDRF) is an important endogenous modulator of vascular tone and platelet function. Although originally believed to be identical to nitric oxide radical (NO°), recent reports suggest that EDRF may consist of a mixture of various nitric oxide species. In addition, the vasorelaxant effects of EDRF are inhibited by the thiol cysteine (Cys), while those of nitric oxide radical are not. Although the one electron reduction product of nitric oxide, nitroxyl anion (NO-) has previously been shown to possess vasorelaxant properties and to be inhibited by Cys, little is known about its interaction with platelets. Therefore we tested the effect of different nitric oxide species [nitroxyl anion, nitric oxide radical and nitrosonium, (NO+)] on platelet aggregation as well as the influence of thiols [Cys and homocysteine (Hcy)] on the interaction.
Methods: Platelet aggregation was performed on platelet-rich plasma prepared from blood samples from healthy adult volunteers. Nitroxyl anion derived from Angelis' salt inhibited ADP-induced (5-10 μM) platelet aggregation in a dose-dependent manner; total inhibition of aggregation occurred at 50 μM, with threshold effects at 1.0 μM. Nitrosonium from S-nitroso-glutathione and nitric oxide radical from diethylamine NONOate were more potent inhibitors of platelet aggregation with threshold effect at 0.01 and 0.1 μM, respectively. Cys (500 μM) significantly decreased the inhibitory effect of 10μM nitroxyl anion ($p>0.03$), but did not affect the responses of either nitrosonium (1μM) or nitric oxide radical (0.1 μM). Hcy (500 μM) did not affect the inhibitory response of any nitric oxide species tested. Cys (500 μM) or Hcy (500 μM) alone did not inhibit platelet aggregation. The higher (L-cysteic acid) and lower (cystine) oxidative forms of Cys had no affect on nitroxyl anion responses. Similar results were obtained for homocyteic acid and homocystine. Interestingly, Cys did not effect the increase in intraplatelet cGMP content produced by either nitroxyl anion or the other nitric oxide species.
Conclusion: Although nitroxyl anion is a less potent inhibitor of platelet aggregation than either nitrosonium or nitric oxide radical these data confirm that like EDRF, nitroxyl anion is inhibited by Cys. These results suggest that the interaction between nitroxyl anion and Cys may lead to a decrease in bioactive EDRF.

P3030 Activated protein C (APC) modulates the expression and release of monocyte chemoattractant protein-1 (MCP-1) in cultured human endothelial cells

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Background: Monocyte chemoattractant protein-1 (MCP-1) plays a critical role in recruiting monocytes to stressed endothelium as an early response to vascular injury. MCP-1 has been reported to be protective under inflammatory conditions such as sepsis and to favor production of antiinflammatory and immune-stimulating cytokines. The activated protein C (APC) pathway has been suggested to be a common link between coagulation and inflammation. In addition to its anticoagulant properties, APC may also function to restore hemostasis via cytokine/chemokine induction, thereby amplifying the local inflammatory reaction. The aim of this in vitro study was to determine the effect of APC on the expression and release of chemokine MCP-1 in human umbilical vein endothelial cells (HUVEC) and to investigate posssible intracellular mechanisms being involved.
Methods: HUVEC were treated with human APC (2.5-10μg/ml) either alone or in combination with tumor necrosis factor-alpha (TNF-alpha 0.1-1ng/ml). MCP-1 was analyzed in supernatants by ELISA and MCP-1-mRNA was determined by a colorimetric mRNA quantitation assay (Quantikine-assay®). The activities of fifty-four different transcription factors in nuclear extracts were analyzed by a protein/DNA array.
Results: APC stimulated MCP-1-gene transcription and MCP-1-protein-synthesis in a time and dose dependent manner: MCP-1-gene transcription was up-regulated compared to controls after 1 hour of incubation with APC. MCP-1 was detected in HUVEC-supernatants as early as 2 hours after the addition of APC and continued to increase through the 24h incubation period. Transcription factor arrays suggested that neither NF-kappa B nor AP-1 were involved in APC's effect on MCP-1-expression. TNF-alpha stimulated mRNA transcription and release of MCP-1. HUVEC pretreated with APC for one hour strongly enhanced the TNF-alpha-stimulated MCP-1 release.
Conclusion: By modulating mRNA-transcription and protein synthesis of MCP-1 in endothelial cells APC contributes to leukocyte trafficking and adherence at the site of vascular injury. Thereby APC may aid in the local inflammatory reaction and may modulate initiation and progression of atherosclerotic lesions.

P3031 Endothelial dysfunction in myocardial inflammation affects patients with and without left ventricular dysfunction

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Objective In myocardial biopsies of patients with myocarditis, endothelial activation can be detected by immunhistology. We hypothesize, that the inflammatory process leads to coronary and peripheral arterial endothelial dysfunction. Further, the impact of left ventricular function (LV-F) on endothelial function in these patients is examined.
Methods Endothelial function of the radial artery was assessed in 34 patients with myocardial inflammation (InfCM) and 10 healthy subjects. By use of high resolution ultrasound, endothelium dependent, flow mediated vasodilation of the radial artery was examined in response to reactive hyperemia. To exclude impairment of vascular smooth muscle cell reactivity, we also tested endothelium independent vasodilation by applying an exogenous NO donor (trinitroglycerin). Left ventricular function was assessed by LV-angiogramm and echocardiography. Patients with arteriosclerotic risk factors were excluded from this study.
Results Mean age of the 34 patients was 47±13 years, 14 were male, 20 female, mean left ventricular ejection fraction (EF) was 57±19%. Mean age of the 10 controls was 43±15 years, sex distribution was equal, EF was normal. Endothelial function of the radial artery, as assessed by flow mediated vasodilation (FMD), was significantly impaired in patients with InfCM (FMD 4.3±3.1%), as compared to controls (FMD 10.4±16%) ($p<0.001$). Endothelial dysfunction in patients with InfCM was more pronounced in patients with impaired LV-F (n=16, EF 40±15%, FMD 2.5±2.7%), as compared to patients with normal LV-F (n=18, EF 71±7%, FMD 5.7±2.6%) ($p<0.001$). Endothelial function correlates with left ventricular function. However, endothelial dysfunction was also significantly impaired in patients with InfCM and normal LV-F (FMD 5.7±2.6%) as compared to controls ($p<0.001$). Endothelium independent vasodilation was preserved in patients with InfCM (GTN-MD 28±8%).
Conclusions Endothelial function is impaired in peripheral arteries of patients with InfCM, even when left ventricular function is normal. This is likely to be caused by the inflammatory response in the endothelium and can be potentiated by other factors with impact on endothelial function, like left ventricular function. Endothelial dysfunction in InfCM is not restricted to the coronary arteries, but is systemic.

P3032 C-reactive protein induces endothelial cell migration via activation of distinct chemotactic signaling pathways

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C-reactive protein (CRP) is a pluripotent mediator of inflammation, and is present at sites of vascular injury and in atherosclerotic lesions. CRP stimulates endothelial cell adhesion molecule expression and monocyte migration, and thereby contributes to the development and progression of vascular lesion formation. In addition to these inflammatory processes, endothelial cell (EC) migration is also involved in the pathogenesis of atherosclerosis, since it plays a major role in the neovascularization of the atherosclerotic plaque. It was the aim of this study to investigate the role of CRP in endothelial cell migration and the chemotactic signaling pathways involved. CRP (0.1-10 ng/ml) induced migration of cultured human umbilical vein EC in a dose-dependent manner (maximal 3.5-fold at 10 ng/ml, $p<0.05$) after incubation for 5 h in a transwell chamber system. Previous studies have shown that EC migration in response to other chemoattractants requires activation of several protein kinases including p42/44 MAPK, p38 MAPK, myosin light chain kinase (MLCK), Akt and eNOS. Using the pharmacological p42/44 MAPK pathway inhibitor PD98059 (30 μM) or the MLCK inhibitor ML7 (1 μM), we observed a significant inhibition of CRP-induced EC migration by more than 90% for each inhibitor (all $p<0.05$). CRP-stimulated EC migration was also dramatically inhibited by the PI3-Kinase->Akt->eNOS-pathway inhibitor wortmannin (-94% at 100 nM, $p<0.05$), whereas the p38 MAPK inhibitor SB203580 (1 μM) had no effect on EC migration. Immunoblotting with phosphospecific antibodies revealed the rapid and transient activation of p42/44 MAPK and MLCK by CRP (10 ng/ml) within 15 minutes, which was completely blocked by PD98059 (30 μM). In contrast, wortmannin did not affect CRP-induced p42/44 MAPK-, or MLCK-phosphorylation. However, CRP-stimulated phosphorylation and activation of Akt and eNOS, which reached maximal responses in EC within 30 minutes, were potently inhibited by wortmannin (100 nM). PD98059 had no effect on Akt- or eNOS-phosphorylation.
Our results indicate, that early activation of two distinct chemotactic signaling pathways, the p42/44 MAPK->MLCK- and the PI3-Kinase->Akt->eNOS-pathway, are essential for CRP-induced EC migration.

P3033 Azithromycin treatment improves endothelial function in patients with coronary artery disease and evidence of chlamydia pneumoniae infection

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Background: It has been suggested that infection with Chlamydia pneumoniae (CPn), can trigger inflammatory mechanisms that may, in turn, impair vascular endothelial function. The aim of the present study was to assess whether treatment with the macrolide antibiotic azithromycin improves endothelial function in patients with coronary artery disease (CAD)and positive antibodies to CPn.
Methods: We carried out a randomised, prospective, double blind, placebo-controlled trial in 40 male patients (mean age of 55±9 years) with angiographically documented CAD and positive CPn-IgG antibody titers (>1:16). After baseline evaluation, patients were randomized to receive either azithromycin or placebo for 5 weeks. Flow mediated dilatation (FMD) of the brachial artery, E-selectin, von Willebrand factor (vWF) and C-reactive protein (CRP) levels were assessed at study entry and at the end of the treatment period.
Results: Baseline evaluation showed that there were no significant differences between the 2 groups of patients treated with azithromycin or placebo regarding patients' age, body mass index, the presence of traditional risk factors and medication including lipid-lowering drugs, as well as glucose and lipid levels.Baseline FMD was also similar in azithromycin and placebo groups (2.66±1.89% vs 3.11±2.06%, P=0.47). Repeated FMD measurements showed that patients who received azithromycin had a significant improvement in FMD (mean change: 2.1±1.1%, $P<0.005$) after 5 weeks of treatment. In contrast, FMD was not significantly changed in the placebo group (mean change: -0.02±0.2%, P=0.64). Azithromycin therapy also resulted in a significant decrease of E-selectin and vWF levels. CRP levels were not significantly altered by treatment with either azithromycin or placebo.
Conclusions: Our findings indicate that treatment with azithromycin has a favorable effect on endothelial function in patients with documented coronary artery disease and evidence of CPn infection. Whether these favorable actions of antibiotic treatment will translate into a beneficial effect on atherogenesis and cardiac events, needs further investigation.

P3034 IL-1RN (VNTR) gene polymorphism predicts a proinflammatory endothelial cell phenotype in HUVEC-Implications for atherogenesis and plaque rupture

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Background: Carriage of allele *2 IL-1RN(VNTR) is associated with angiographic single vessel coronary artery disesae(Francis et al Circ 1999) but the mechanisms are not understood. Interactions between monocytes & endothelial cells (EC) play a significant role in the pathogeneis of atherscIerosis & plaque rupture. These processes may involve an increased expression of adhesion molecules e.g. E-selectin, in response to proinflammatory cytokines which are abundant in atherosclerotic plaques. IL-1RN(VNTR) *2 carriage, results in reduced intracellular levels of IL-1ra in HUVEC (Dewberry et al ATVB 2000. A 1000 fold excess of IL-1ra is required to antagonise the actions of IL-1. We hypothesised that carriage of *2 IL-1RN (VNTR) might result in an inflammatory EC phenotype. Methods: HUVEC were cultured in 24 well plates & genotyped for IL-1RN(VNTR). At confluence they were stimulated with 0.1, 1 and 10ng/ml of IL-1beta for 6 & 24 hours. E-selectin levels were measured in the cell lysate & in the supernatant using an ELISA kit(R&D systems). The association of the homozygous forms of the rarer *2 & common 1 allele, with E-selectin expression, were compared by an unpaired t-test.Results: IL-1 beta significantly increased the expression of E-selction in the cell lysate compared with unstimulated cells for either genotype at 6 & 24 hours. There was no significant difference between the 3 different doses of IL-1 beta on E-selectin expression in the lysate. Levels rose after 6hrs & then fell at 24hrs in both genotypes. However the 2,2 genotype was associated with increased expression of E-selectin for each dose of IL-1 beta compared with the 1,1 genotype(132.5 ± 27.88, 126.25 ± 1.28 & 152.58 ± 6.11ng/ml cf 75.32 ± 3.78, 71.99 ± 8.21 & 67.36 ± 6.48ng/ml respectively: p=0.09, 0.02 & 0.02 respectively) at 6 hours and at 24 hours (27.49 ± 2.86, 32 ± 1.78 & 26.7 ± 5.18ng/ml cf 12.29 ± 0.74, 11.07 ± 0.3 & 13.1 ± 1.42ng/ml respectively: p=0.04,0.007 & 0.1 respectively).Conclusions: Our data suggests that the homozygous form of the rarer *2 allele of IL-1RN(VNTR) is associated with an exaggerated expression of adhesion molecules in response to inflammatory stimuli. This may result in the increased accumulation of inflammatory cells at specific sites. We postulate that this mechanism could result in increased atheroma formation in stable coronary disease (Francis et al) or lead to palque rupture in inflamed vulnerable plaques. Our data also suggests that the release of soluble E-selectin from the cell surface into the supernatant may require more than one stimuli such as activated neutrophils.

P3035 BH4 improves endothelial function after ischaemia/reperfusion

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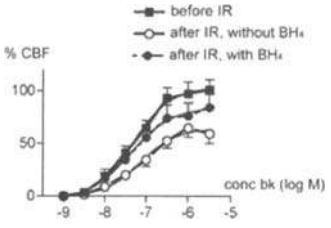
Background: Reperfusion after myocardial ischemia augments tissue injury in excess of that produced by ischemia alone, and leads to coronary endothelial dysfunction. Amelioration of endothelial dysfunction after myocardial ischemia represents an attractive goal for therapeutic interventions to reduce symptoms or clinical events. This study was designed to determine whether tetrahydrobiopterine (BH4) improves endothelium-dependent coronary vasomotion after ischemia/reperfusion (IR). BH4 is an essential cofactor of nitric oxide synthase (NOS) and a scavenger of oxygen-derived free radicals. Decreased availability of BH4 leads, under in vitro conditions, to reduced NO production and increased superoxide formation. BH4 improves endothelial function in patients with cardiovascular risks or with chronic coronary artery disease, but it has never been proven that BH4 ameliorates endothelial disfunction after ischemia/reperfusion injury.
Methods and results: Vasoresponses to bradykinine (bk, 50×10^{-6} l, 10^{-9} to 10^{-5} M) were recorded in isolated Langendorff perfused rat hearts (n=12), before and after ischemia/reperfusion (15/30 min.).
BH4 (10^{-2} M) was added to the perfusate of during reperfusion (n=7). The vasodilator responses to bk after reperfusion (% of coronary bloodflow, CBF) were very significantly improved (p<0,0001, ANOVA)



Conclusion: Administration of BH4 during reperfusion reduces endothelial dysfunction after IR. This observation may represents a new therapeutic option in patients with a recent myocardial infarction.

P3036 Risk/benefit ratio of revascularisation versus medical therapy in chronic coronary artery disease of the elderly

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Background: The mortality risk of revascularisation increases with age. To determine the revascularisation risk in relation to the risk of medical therapy in elderly patients (pts) during a 1-year follow-up, we analyzed all 176 pts of the prospective TIME study in whom revascularisation was attempted (REVASC) and compared them to all 125 pts who received medical treatment alone (MED) (on-treatment analysis).
Methods: The REVASC group consisted of 112 pts randomized to PCI or CABG and 64 pts initially randomized to medical therapy but needing PCI or CABG during follow-up. The MED group consisted of 84 pts randomized to medical therapy who stayed on that therapy and 41 invasive pts who were not revascularized (revascularisation not possible, refused or no coronary artery disease). All pts had quality of life (QoL) and angina severity assessed by questionnaire at baseline and after 1 year.
Results: Baseline characteristics of REVASC and MED pts were similar with an age of 80±4 years and 40% vs. 49% women (p=ns). After 1 year, total mortality was 9.7% vs. 9.6%, and cardiac mortality 6.8% vs. 8.8% (REVASC vs. MED, p=ns). The corresponding cardiac death/myocardial infarction (MI) rates were 15.3% vs. 12.8% (p=ns). REVASC pts improved angina severity and measures of QoL significantly more than MED pts (p<0.01). The 34% of pts treated by CABG differed from PCI pts in the rate of hypertension (78% vs 56%, p<0.01) and of 3 vessel disease (88% vs. 53%, p<0.0001), whereas left ventricular ejection fraction was not significantly different (60±13% vs. 55±16%, p=ns). PCI pts had a similar 30 d cardiac mortality (2.6% vs. 3.3% after CABG) and 1 year cardiac death/MI rate (16.4% vs. 13.3%) as compared to CABG pts; however, angina severity decreased and QoL increased significantly more after CABG (p<0.01).
Conclusion: In this prospective on-treatment analysis, pts with REVASC had no increased cardiac mortality risk compared to MED treated pts but a greater improvement in QoL and angina. PCI in pts selected for suitable anatomy for PCI had a similar early mortality and 1 year death/MI rate as CABG surgery; however, the benefit in QoL and angina was smaller.

DRUG THERAPY IN HEART FAILURE

P3037 Efficacy and safety of tadalafil in men with erectile dysfunction: an integrated analysis of registration trials

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Purpose: Tadalafil is a selective and potent inhibitor of phosphodiesterase type 5 for the treatment of men with erectile dysfunction (ED). In the presence of sexual stimulation, tadalafil has been shown in clinical trials to enable men with ED to achieve and maintain erection sufficient for successful intercourse. This integrated analysis was undertaken to assess the efficacy and safety of tadalafil.
Methods: Tadalafil doses of 2.5 to 20 mg, taken as needed up to once daily, were evaluated in 5 (four 12-week; one 24-week) randomized, double-blind, placebo-controlled Phase 3 trials enrolling 1112 men (mean age, 58 years; range, 21-82 years). Patients were free to choose the time of sexual attempts after dosing, and to take the medication with no restrictions on food and alcohol intake. Three widely used, self-administered instruments (International Index of Erectile Function, Sexual Encounter Profile diaries, and Global Assessment Question) were used to evaluate treatment effects.
Results: Compared with placebo, tadalafil significantly improved all primary and secondary endpoints. Up to 81% of tadalafil-treated men (n = 972 from the four 12-week studies) reported improved erections. The mean percentage of successful intercourse attempts improved to up to 75%. Efficacy was consistent in each of these studies and in mild-to-severe ED of psychogenic, organic, or mixed etiology. The adverse events (AEs) reported with tadalafil were generally mild-to-moderate in intensity, were transient, and attenuated with continued dosing. Discontinuation rates were similarly low in tadalafil- and placebo-treated patients. Headache, dyspepsia and back pain were the most commonly reported AEs (>5%) across studies.
Conclusion: Findings of these studies support the conclusion that on-demand tadalafil is a well-tolerated treatment that significantly improves erectile function in men with mild-to-severe ED. These data suggest that tadalafil may become an important new treatment option for men with ED.

P3038 Efficacy of beta-blockers in diabetic patients after myocardial infarction. From silent left ventricular dysfunction to overt heart failure

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Diabetes is a powerful risk factor for an adverse outcome during the acute phase and after myocardial infarction (MI). In spite of their proved efficacy beta blockers are still underused after MI. We analysed the long term effect of beta blockers in diabetic patients (pts) with LV dysfunction or overt heart failure (HF) early after MI. Among 3424 pts admitted to our CCU with acute MI from 1992 to 2001, 600 (17,5%) had diabetes mellitus. In-hospital mortality (11 vs 6.6%,p<0.0001), Killip class >1 (15 vs 5%,p<0.0001) and LV dysfunction, as measured by 2-D echo EF<40% (30 vs 11%,p<0.0001) were all more frequent in diabetic vs non diabetic pts. Diabetes was an indipendent predictor of all these complications at multivariate analysis. Beta-blocking drugs were administered to 69% of pts with LV dysfunction (125/180) and to 40% HF patients (36/90), with a steep increase of the percentage in the last four years (p<0.0001 vs 1992-1997). Inability to reach a stable clinical cardiovascular status, severe bronchospastic pulmonary disease or peripheral vascular disease, bradycardia or hypokinetic arrhythmias uncorrected by pacemaker implantation, clinically significant hypotension were the only contraindications to therapy. The beta-blockers used, with slow, gradual and progressive dose titration were metoprolol up to 200 mg, atenolol up to 100 mg and carvedilol up to 50 mg. Worsening of clinical status necessitating the interruption of therapy ensued in 11.1% (4/36) HF and 6.4% (8/125) LV dysfunction pts. At 1-year follow-up, diabetic pts who received beta-blockers had a lower total mortality (4 vs 9%, p<0.0001), incidence of presumed sudden cardiac death (1 vs 5% p<0.0001), acute MI (2 vs 6%, p<0.001), a lower progression to clinical HF (6 vs 14%, p<0.0001), less hospitalizations (5 vs 13%, p<0.0001), a lower need for ICD implantation (1 vs 3%, p<0.05) and CABG (12 vs 18%, p<0.05). Beta-blockers were indipendent predictors of all these outcomes at multivariate analysis. The comparison of different periods of time (beta-blockers were administered mainly during the last four years) with global differences in patients' treatment may be a significant limit of our observations. Nevertheless, at intermediate follow-up beta-blockers do exert a beneficial effect on clinical hard end-points and are also cost-effective in preventing costly outcomes. Our data suggest that a trial of beta-blocking therapy is worth in most diabetic patients with LV dysfunction or clinical HF early after MI.

P3039 Effects of nebivolol on myocardial performance after long-term treatment in heart failure patients: a double-blind, placebo controlled study

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Background: Beta-adrenergic blocking drugs have been shown to have beneficial effects on patients (pts) with heart failure. Nebivolol, a new, third generation, selective beta 1- blocking agent, that possesses a peculiar pharmacodynamic profile, has not been widely studied.
Objectives: The purpose of our study was to examine the long-term (3 months) effects of Nebivolol on cardiac systolic and diastolic function in patients with Idiopathic Dilated Cardiomyopathy (IDC).
Methods: Sixty patients, aged 55±9.5 y, with angiographically proven IDC, ejection fraction (EF)<45%, in stable New York Heart Association (NYHA) class II-III, entered a double-blind, randomized Nebivolol and placebo-contolled trial. Variables of left (LV) and right (RV) ventricular function at baseline and after 3 months of oral administration of Nebivolol (1,25 to 5 mg/day in four weeks) or placebo were assessed echocardiographically.
Results: There were no significant baseline differences regarding NYHA class, heart rate (HR), LVEF, systolic blood pressure (BP) or echocardiographic variables between the 2 groups. During follow-up, 4 pts in the Nebivolol (13,3%) and 5 (16,6%) in the placebo group discontinued the medication because of symptoms aggravation or significant hypotension. After 3 months of Nebivolol treatment, there was a decrease in resting HR (74,2±8, vs 69,2±8,4,p=0,05) and systolic BP (144.8±12,1 vs 119,6±9,7 mm Hg p<0,001)and a significant increase in LVEF (33,1 ±10% vs 38,8% ±7.3, p=0,04), mainly due to decreased end-systolic volume (104±35 ml vs 88.4±30.5 ml, p=0,03) while the LV diastolic volume showed a slight decrease (151,6±40,8 vs 140,6±37,7 ml, p=NS).
Left ventricular systolic wall stress also decreased (193,4± 44,3 vs 161,7±36.8 Kdynes/cm^2, p=0,06) and the right ventricular EF increased significantly (40,3±8,7vs 50,9±9,3%, p=0,04).Indices of diastolic LV function also improved. The velocity time integral of late LV filling increased (5,5±1,3 vs 7,3±2,1 cm, p=0,01) while the pulmonary veins atrial wave, decreased significantly (0,39±0,06 vs 0,29±0,04 cm/sec, p=0,01). There were no significant differences in the placebo group at 3 months concerning all aforementioned parameters.
Conclusion: Nebivolol is an effective and relatively safe treatment in idiopathic dilated cardiomyopathy. After 3 months of treatment, there was an improvement in LV and RV systolic function, with evidence of increased intrinsic contractility, while beneficial effects on LV diastolic function indices were found.

P3040 Prescribing for heart failure in general practice: the relationship between physician knowledge and prescribing quality

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Objectives: To investigate the relationship between different aspects of GP knowledge of the drug groups (diuretics, angiotensin converting enzyme inbibitors, beta-blockers, digoxin, spironolactone and angiotensin II antagonists) commonly used to treat chronic heart failure (CHF) and their actual use of these agents in daily practice.
Design: Cross-sectional survey: GP questionnaire and patient chart review.
Setting: General Practice
Participants: 78 GPs and 769 CHF patients participating in the IMPROVEMENT study.
Main outcome measures: GP knowledge was assessed by a questionnaire covering 3 domains: awareness of the current evidence, perceptions of how often each agent should be used for CHF and indications and contraindications. Current practice was assessed by the percentage of patients per GP prescribed each drug group.
Results: No relationship between knowledge and actual use of a drug group was observed for any of the 3 domains. Knowledge regarding the current evidence and how often a drug group should be used for CHF were high while knowledge regarding indications and contraindications was lower. No correlation between the 3 knowledge domains was found.
Conclusions: GP knowledge of the current evidence for the drug groups commonly used in CHF, with the exception of the beta-blockers, was good. A knowledge deficit was identified regarding the indications and contraindications for each drug group. No relationship between knowledge and actual use was found indicating that interventions addressing the use of CHF drugs in daily practice could be more useful in bridging the gap between evidence and practice than interventions that simply concentrate on improving GP knowledge.

P3041 Urine pH decreases strikingly in response to the loop diuretic torasemide

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Background: Measures should be adopted to avoid the development of acidosis in patients with heart failure (HF). Furosemide (Fur) decreases urine pH mildly, and potassium-retaining diuretics alkalinize the urine and thus tend to cause acidosis. At variance with Fur, torasemide (T) does not inhibit carbonic anhydrase in the nephronal proximal tubule and thus may be expected to reduce urine pH markedly. The aim of this study was to assess the response of urine pH to an amount of T that is frequently prescribed to be taken once daily in HF.
Methods: Fourteen healthy subjects (age range: 20-26) in a metabolic unit took single oral doses of placebo and of T 20 mg, at 08.00 hours, on two conveniently separated single-treatment days. The design was individually randomised, crossover and double-blind. Data are presented as mean ± SD. Mean values were compared by the t test for paired samples.
Results: Urine pH was 5.76 ± 0.44, 6.54 ± 0.66, 6.62 ± 0.57, 5.99 ± 0.40, 6.17 ± 0.58 and 5.70 ± 0.37 in urine collected 0-1.5, 1.5-3, 3-6, 6-9, 9-12 and 12-24 h after dosing with placebo, respectively. Corresponding values after dosing with T 20 mg were 5.35 ± 0.65, 4.97 ± 0.63 ($p < 0.001$ vs. placebo), 4.93 ± 0.66 ($p < 0.001$), 4.93 ± 0.42 ($p < 0.001$), 5.39 ± 0.60 ($p < 0.001$) and 5.34 ± 0.24 ($p < 0.001$). Urinary sodium excretion was 14 ± 5, 11 ± 4, 27 ± 16, 30 ± 11, 32 ± 14 and 66 ± 25 mmol over the 0-1.5-, 1.5-3-, 3-6-, 6-9-, 9-12- and 12-24-h periods after dosing with placebo. Corresponding values after dosing with T 20 mg were 125 ± 23 ($p < 0.001$), 98 ± 22 ($p < 0.001$), 54 ± 25 ($p < 0.05$), 17 ± 11 ($p < 0.05$), 9 ± 4 ($p < 0.001$) and 19 ± 7 ($p < 0.001$).
Conclusion: T 20 mg reduced urine pH values throughout the 1.5-3-, 3-6-, 6-9-, 9-12- and 12-24-h post-dosing periods. Urine pH mean values fell by 1.06-1.69, with respect to post-placebo urine, between 1.5 and 9 h after administration of T 20 mg, and they decreased by 0.36-0.78 between 9 and 24 h after dosing. In a similar study that we carried out on fourteen healthy subjects, Fur 40 mg reduced pH only in urine collected between 1.5 and 3 h after dosing and by a mean value of only 0.3. Thus, T 20 mg could decrease serum pH by more than equinatriuretic amounts of those loop diuretics that also act on the proximal tubule (Fur, bumetanide and piretanide) in patients with HF. This possibility merits research, and it is worthy of consideration in the treatment of HF patients who are prone to develop acidosis, including type 1 diabetics, individuals also receiving spironolactone and/or amiloride, and elderly subjects.

AORTIC VALVE STENOSIS

P3042 Assessment of aortic valve calcification allows risk stratification in mild and moderate aortic stenosis

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Background: The degree of aortic valve (AV) calcification has been shown to be a significant predictor of outcome in severe aortic stenosis (AS). In addition, aortic sclerosis has recently been reported to be associated with a significant increase in mortality. However, it remains unknown whether the degree of AV calcification is of prognostic value in mild and moderate AS.
Methods: 176 consecutive patients (73 female, age 58±19 yrs) who were found to have mild to moderate AS defined by a jet velocity between 2.5 and 4.0 m/s in 1994 were followed for 51±18 months. The degree of AV calcification and other risk factors were assessed. The rate of hemodynamic progression was determined and the clinical outcome was analyzed.
Results: Kaplan-Meier event-free survival for the entire patient group, with endpoints defined as death (n=34) or aortic valve surgery (n=33) indicated by the development of severe symptomatic AS, was 95±2% at 1 yr, 75±3% at 3 yrs, and 60±5% at 5 yrs. Presence of moderate or severe AV calcification, presence of coronary artery disease and peak aortic jet velocity (AV-Vel) at entry were significant independent predictors of outcome ($p<0.0001$, $p<0.001$ and $p<0.01$, respectively). Event-free survival for patients with moderate or severe valve calcification was 92±4% at 1 year, 61±7% at 3 and 42±7% at 5 years versus 100%, 90±4% and 82±5% for patients with no or mild calcification. Diabetes, hypercholesteremia and arterial hypertension were not significant predictors of outcome. The mean rate of hemodynamic progression was significantly faster for patients with an event (0.43±0.04 m/s/yr) than for those without an event (0.14±0.02 m/s/yr, $p<0.0001$). Of 129 patients with a follow-up echocardiographic exam, 59 (46%) developed severe AS (AV-Vel > 4 m/s) during follow-up. 15 cardiac and 19 non-cardiac deaths occurred. Mortality was 1.8 times higher than that of an age and gender - matched control population ($p<0.005$).
Conclusion: Rapid progression to severe AS and an increased mortality have to be considered in mild and moderate AS. In particular, patients with significant calcification of their AV but also those with coronary artery disease and patients in whom serial echocardiograms reveal a rapid progression of the aortic jet velocity have a poor outcome. Thus, moderate and even mild AS cannot be considered a benign disease. Serial Doppler studies and the assessment of valve calcification are crucial for the management of these patients as they identify high-risk patients who require closer follow-up than currently recommended.

P3043 Operative risk in patients with severe aortic stenosis

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Background: Some authors suggest patients with asymptomatic aortic valve stenosis should undergo aortic valve replacement (AVR). However, no consensus has been reached as regards this indication since valve replacement mortality is higher than that of the natural evolution of the disease.
Objective: To identify populations with low operative risk among patients undergoing elective AVR for symptomatic severe aortic stenosis.
Methods: From June 1996 to February 2001, 2,100 patients underwent valvular replacement. Severe aortic stenosis was present in 934 patients (44%). Mean age was 68±13 years; 373 patients (41%) were female. Outcomes of isolated AVR or combined with mitral valve replacement (RVM), coronary artery bypass graft (CABG) or more than two procedures were analyzed. Parsonnet stratification score was used to assess operative risk.
Results: Multivariate analysis showed: age p=0.01, female sex p=0.01, combined AVR p=0.002, reoperation p=0.002, severe LVSF p=0.01. Parsonnet 5 (43 patients, 5%), identified a subset without operative mortality, between 6 and 10 (384 patients, 41%) mortality was 2.6% (10 patients), between 11 and 15 (310 patients, 33%) was 7% (22 patients), and higher than 15 (256 patients, 21%) was 15% (38 patients) (p=0.0001).

	AVR	AVR+CABG	AVR+MVR	AVR+Other
N	489	331	49	65
Age	63.5±13	69±8	56±12	65±12
Severe LVSF	12.6%	13.9%	6%	17%
NYHA FC	2.2±0.9	2.4±0.8	2.5±0.7	2.1±0.9
Parsonnet score	8.2±3.3	13±5.1	13±5.4	17.6±10
Mortality	3.1%	9%	5.5%	11%

LVSF=left ventricular systolic function; NYHA FC= New York Heart Association functional class

Conclusion: Patients <70 years of age, male sex, and without coronary artery disease or other heart valve disease had the lowest hospital mortality (Parsonnet score 5). Parsonnet score is useful to identify different operative risks in populations with aortic stenosis.

P3044 Association of coronary artery disease with aortic valve calcification and calcified plaque in the thoracic aorta

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Aortic valve calcification and coronary atherosclerosis share many risk factors and a possible association of aortic valve calcification with coronary artery disease (CAD) has been suggested. It has also been showed that the presence of aortic atheromas detected by transesophageal echocardiography is strongly associated with CAD. The purpose of this study was to evaluate the relation between calcification of the aortic valve, calcified plaques in the thoracic aorta and CAD in patients undergoing coronary angiography.
Methods: Consecutive 1100 patients (771 men, age 63±11 years) undergoing elective coronary angiography were evaluated by echocardiography for the presence of aortic valve calcification. Chest x-rays was used to detect calcified plaques in the thoracic aorta. Aortic calcified plaques were considered present when typical calcific densities were seen in the aortic arch or in the descending part of the thoracic aorta.
Results: Of the 1100 patients included in the study, 812 (73.8 percent) had CAD, and 288 (26.2 percent) had normal coronary arteries. Aortic valve calcification was present in 420 (38%) and aortic calcified plaques in 180 (16%) of the entire study population. The patients with aortic valve calcification had a significantly higher prevalence of CAD (88% vs 65%, $p<0.0001$) and higher rates of multivessel disease (65% vs 55%, p=0.003). Also, the prevalence of CAD (86% vs 71%, $p<0.0001$) and multivessel disease (66% vs 57%, p=0.035) were significantly higher in patients with aortic calcified plaques compared the patients without aortic calcified plaques. Logistic regression analysis showed that aortic valve calcification (p=0.003) and aortic calcified plaques (p=0.004) were strongly and significantly associated with CAD after adjusting for coronary risk factors. In addition, patients with aortic valve calcification had a high incidence of aortic calcified plaques (23% vs. 12%, $p<0.0001$).
Conclusions: We found a significant association of CAD with the presence of aortic valve calcification and aortic calcified plaques. Our study further demonstrates that aortic valve calcification are significantly associated with calcified plaques in the thoracic aorta. Therefore, it is reasonable to suggest a common etiologic basis for these calcifications and coronary atherosclerosis, and their presence should be regarded as a sign for the presence of CAD.

P3045 Aortic stenosis and haemorrhagic syndrome: close correlation between severity of AS and acquired abnormalities of von Willebrand factor

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Background: Hemorrhagic syndrome has been previously reported in severe aortic stenosis (AS), related to abnormal proteolysis of von Willebrand Factor (VWF). However, little is known about physiological determinants as well as clinical consequences of these abnormalities of VWF.
Methods: We prospectively enrolled 47 patients (70±10 yrs) with moderate (mAS, 7) or severe (sAS, 40) AS. Forty patients with sAS underwent subsequent aortic valve replacement. History of bleeding events was recorded in each case and severity of AS was evaluated in echocardiography. Selected parameters of primary hemostasis reflecting VWF abnormalities (closure time of PFA 100® (CTADP), VWF:Ag, VWF:CB, and multimeric analysis of VWF) were evaluated in all patients, with early (day 1 and 7) and late (6 months) postoperative assessment in sAS.
Results: Aortic orifice area and mean transvalvular gradient were 0.67±0.17 cm^2 and 58±12 mmHg in sAS, compared with 1.14±0.17 cm^2 and 32±11 mmHg (both $p<0.01$) in mAS. In sAS, 33% (14/40) of patients presented recent history of bleeding, and 76% had prolonged CTADP. In mAS 29% of patients had prolonged CTADP, but mean CTADP was significantly longer in sAS compared with mAS (193±64 vs 121±32 s, p=0.01). Plasma level of VWF:Ag was in the normal range in all patients. Four patients with sAS had decreased level of VWF:CB. The percentage of high molecular weight multimers (%HMW multimers) of VWF was decreased in sAS, compared with mAS ($p<0.05$). Nevertheless, abnormal multimeric profile was also observed in mAS. Interestingly, for overall patients there were a highly significant correlation between either mean transvalvular gradient or stenosis-induced shear stress and CTDAP (both r=0.54, p=0.001). History of preoperative bleeding and severity of VWF abnormalities (%HMW multimers) were associated with per and early postoperative bleeding in sAS (respectively Chi-square p-value: 0.002, and Mann-Whitney p-value: 0.009). Complete correction of %HMW multimers was obtained the first day after valve replacement.
Conclusion: Our study demonstrate for the first time a close correlation between severity of AS assessed with mean transvalvular gradient or stenosis-induced shear stress and VWF abnormalities, explaining pre and postoperative bleeding. Moreover, abnormalities of VWF may be found also in non surgical AS. Surgical correction of AS result in an early and sustained correction of VWF abnormalities. Consequently, acquired bleeding history in this setting should not contraindicate a mechanical prostheses implantation.

P3046 Clinical interest of brain natriuretic peptide serum levels in aortic stenosis

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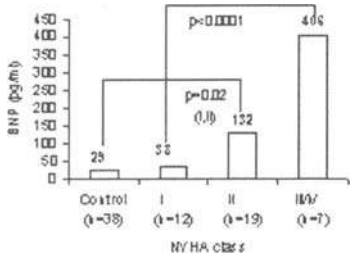
Background: timing of valve replacement in aortic stenosis (AS) is currently based on the presence of symptoms. However, in elderly patients symptoms may be difficult to evaluate and there is no validated parameter indicating the timing of surgery in asymptomatic patient with severe AS. Brain Natriuretic Peptide (BNP) is secreted predominantly from the cardiac ventricles and has been shown to have a diagnostic and prognostic value in congestive heart failure. Few studies have reported its clinical interest in AS.
Methods: Serum BNP levels were measured by radio immunoassay in 38 control subjects and 38 patients with severe AS and normal left ventricular function with concomitant clinical and echocardiographic evaluation.
Results: 18 women and 20 men (mean age, 72 ± 13 years) with a severe AS (mean aortic valve area, 0. 7± 0.1cm^2; mean transaortic pressure gradient, 50 ± 21mm Hg) and preserved left ventricular function (mean left ventricular shortening, 0.38 ± 0.1) were enrolled. Mean BNP values differed significantly between patients according to NYHA functional class with a positive predictive value of 96% to detect symptomatic patients (cut-off value, 65 pg/ml). By single linear regression, BNP value appeared to correlate with aortic time-velocity integral (r = 0.34, p = 0.03) and peak diastolic atrial velocity by tissue Doppler (r = 0.57, p = 0.01). BNP serum levels were not correlated to aortic valve area.



Mean BNP value.

Conclusion: BNP serum level is an objective non invasive parameter witch can be helpful to detect symptomatic patient with AS when clinical evaluation is difficult. Correlation to diastolic and systolic left ventricular echographic parameters may reflect myocardial adaptation to increased afterload.

P3047 Common biological features between calcific aortic valve stenosis and carotid atheromasic plaque: an histological and immunohistochemical study

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Background: Many observations support the hypotesis that calcific aortic valve stenosis is an active and chronic inflammatory process with similar characteristics of atherosclerotic plaque.
Methods: We selected 26 non-rheumatic aortic valves from symptomatic patients (AVA mean value 0.6±0.12cmq) undergoing surgical replacement and the stable carotid artery plaques from 15 previously symptomatic and 22 asymptomatic patients undergoing carotid endarterectomy with >60% stenosis. We performed histological analysis on paraffin-embedded carotid plaque samples and aortic valve leaflets for a semiquantitative assessment of inflammatory cell abundance, neoangiogenesis, atheroma, sclerosis, and calcium. Tissue samples were semiquantitatively analyzed by immunohistochemistry for Intracellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1(VCAM-1)expression.
Results: Calcific aortic valve (A) showed a prominent calcium deposits in nodular form, dense inflammatory lymphocytes infiltrates and neoangiogenesis close to calcium deposits, fibrosis.. Stable carotid plaques (B) showed dense inflammatory cell infiltrates in shoulder atheroma with lymphocytes prevalence and neoagiogenesis, diffuse sclerosis and local calcifications. In both A and B we found thin vessels (wall thickness<10μm) and thinless vessels (wall thickness>30μm). In A angiogenesis was correlated with inflammation (p=0.0007), the most significativity was between thin vessels and local abundance of lymphocytes ($p<0.00001$).Neoangiogenesis correlates with calcium(p=0.003). In B we found a correlation between neoangiogenesis and inflammation (p=0.04) exspecially between thin vessels and lymphocytes infiltrates (p=0.0005). In A and B adhesion molecules (ICAM-1 and VCAM-1) expression was detected on the neovessel cells to confirm the endothelial activation.. In A was found a significative correlation between inflammatory infiltrates and ICAM-1 (p=0.003).
Conclusions: Calcific aortic valve and stable carotid atheromasic plaque showed common areas of biological activity expressed by neongiogenesis associated to inflammatory infiltrates and endothelial activation. Neoangiogenesis may have a role in the plaque evolution as well as in aortic valve stenosis progression.

P3048 Influence of valve orifice variability during ejection on haemodynamics of aortic stenosis: a computer numerical simulation study

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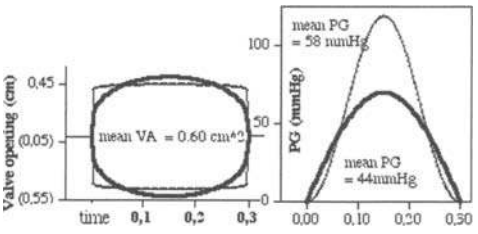
Background: Recent experimental and clinical studies based on high speed video and transesophageal planimetry measurements have reported variations of valve orifice area (VA) during ejection in aortic stenosis (AS) with cusps opening/closing rates (OCR) slower than in normal valves. VA variability during ejection may be different between 2 AS valves due to various degrees of cusps thickness, calcifications and commissural fusion leading to different elastic and inertial properties of the valve. The impact on AS hemodynamics of VA variability during ejection remains unknown.
Methods: Using a computer simulation modeling, we evaluated the impact of AS VA variability during ejection on transvalvular pressure gradients (PG) and on the Gorlin formula derived mean VA. Based on mathematical analysis of patterns reported in the literature, OCR were simulated using a complex powered sine function accounting for mechanical properties ot the valve. The model allowed to make vary the following input: outflow tract velocity profile, outflow tract and ascending aorta diameters, ejection period, mean VA, OCR patterns.
Results: At similar outflow condition and mean VA, VA variability resulted into significant changes in peak and mean PG (range 0%-54% and 0%-32%, respectively). The Gorlin formula accurately predicted VA when VA was constant during ejection but overestimated it up to 32% when maximal opening was delayed to mid-ejection.



Conclusion: Despite similar mean anatomical VA and outflow conditions, stenotic valves with different intrinsic mechanical properties may result into different total afterload burdens and Gorlin formula data due to different VA variability patterns during ejection. This new concept should be taken into account when evaluating AS hemodynamics.Figure

P3049 Importance of left ventricular dynamics/valve orifice matching during ejection for afterload minimization in aortic stenosis. A computer study

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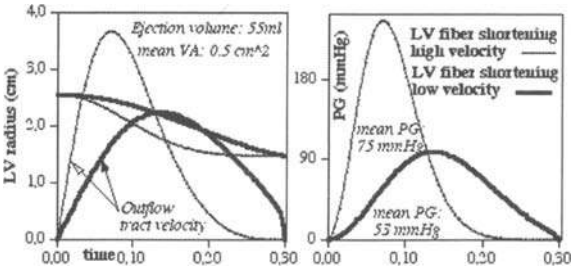
Background: Why outflow tract velocity temporal profile (OVP) in aortic stenosis (AS) is characterized by a slow systolic upstroke with a delayed peak flow remains unknown. Recent experimental and clinical studies based on high speed video plaminetry measurements have reported variations of AS valve orifice area (VA) during ejection due to various degrees of leaflets thickness, rigidity, calcifications and commissural fusion leading to different elastic and inertial properties of the cusps.
Methods: Using a computer simulation modeling, we evaluated the impact of LV dynamics/VA variability ejection coupling on AS transvalvular pressure gradients (PG). Dynamics of LV fiber shortening was computerized using a powered cosine function during ejection. Based on mathematical analysis of patterns observed in clinical studies, VA variability was computer simulated first as a complex sine function of time and then VA(t) to PG(t) relation during ejection was fitted by a curvilinear function accounting for mechanical properties of the valve(r= 0.99-1.00). The model allowed to make vary the following input parameters: LV fiber shortening extent, LV fiber shortening velocity and OVP, outflow tract and ascending aorta diameters, ejection period, mean VA, VA variability.
Results: At similar ejection volume and LV ejection fraction and mean VA, a slower LV fiber shortening velocity resulted into a typical AS OVP with a PG lower than did a normal OVP due to a rapid LV fiber shortening rate.
Conclusion: Slow outflow acceleration with late peak flow as typically observed in aortic stenosis reflects adaptative LV fiber shortening rates in order to optimize LV dynamics/valve coupling and to minimize LV afterload.



P3050 Overestimation of valve area in bicuspid aortic – stenosis by transoesophageal planimetry as a function of jet eccentricity stenosis

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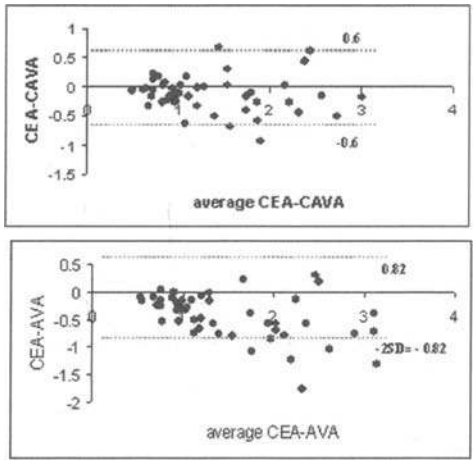
Background: Bicuspid aortic stenosis (AS) is the most frequent congenital anomaly. Because of the 2 cusps arrangement, valve is often obstructive and the stenotic jet eccentric. 2-D transesophageal echocardiography (TEE) has been proposed as a reliable method for determining aortic valve area (AVA) in patients with AS.
Purpose: We sought to compare AVA by TEE planimetry and by Doppler-derived continuity equation (CEA) in patients with bicuspid and tricuspid AS and determine the effect of stenotic jet eccentricity.
Methods: Fifty patients (age 49±15 years) with bicuspid and 22 patients with tricuspid (71±13 years of age) AS undergoing transthoracic (TTE) and TEE were studied. CEA area was obtained from TTE and AVA by TEE as the smallest area during systole. The stenotic jet angle was measured from off-line analysis of the TEE color Doppler images and used to derive an eccentricity index (EI). The cosine of this angle is proposed to correct AVA.
Results: 1) In the tricuspid valve group, there was an excellent correlation between CEA (1.13±0.46cm^2) and AVA (1.15±0.36cm^2) ((r=0.91, p<0.001, delta=0.14±0.13, p=0.37). 2) In the bicuspid group, AVA (1.80±0.93 cm^2) overestimated CEA (1.36±0.77 cm^2, r = 0.89, delta = 0.44 ±0.41 cm^2, p<0.001) EI was 33.4±9.7° (p<0.001 compared to tricuspid group). The agreement between CEA and AVA was improved after correction for the cosine of the angle of the jet (CAVA = AVA∗angle cosine) (figure).



Bland&Altman CEA-CAVA/CEA-AVA.

Conclusion: TEE planimetry of AVA may cause under-estimation of stenosis severity, depending on jet eccentricity. AVA overestimation is attenuated by an adaptation based on the stenotic jet angle cosine (CAVA).

P3051 Reglonal differences in the haemodynamic stress at the ascending aorta in patients with bicuspid and tricuspid aortic valve

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Patients with bicuspid aortic valve have a higher incidence of dilation of the ascending aorta in comparison to the normal population. It is unclear whether it is caused by abnormal hemodynamics or by an underlying congenital aortic wall defect. This echocardiographic study examined the differences in hemodynamic stress at the ascending aorta in patients with bicuspid and tricuspid aortic valve.

Methods: 58 consecutive patients with aortic valve stenosis and either bicuspid or tricuspid valve and an ascending aortic diameter of $\leq$ 4.5cm were divided into two groups: group A (bicuspid aortic valve, 26 patients, age 61 $\pm$ 10 years) and B (tricuspid aortic valve, 32 patients, age 65 $\pm$ 10 years). Preoperative echocardiographic examinations (2-dimensional, M-mode, CW Doppler, aortic wall tissue Doppler) were performed from parasternal long axis view using ALOKA 5.5.

Results: There were no differences between the groups in regard to the diameter of the ascending aorta (38.0 $\pm$ 7.4mm versus 36.1 $\pm$ 4.1mm, p = 0.87), the maximal pressure gradient across the aortic valve (88.0 $\pm$ 11.6mmHg versus 85.1 $\pm$ 13.3mmHg, p = 0.66) or the percentual systolic increase of the ascending aorta diameter (6.2 $\pm$ 2% versus 5.8 $\pm$ 3%, p = 0.9). However, the peak systolic wall velocity in the anterolateral region of the ascending aorta was significantly higher in group A (bicuspid valve) than in group B (tricuspid valve) (12.2 $\pm$ 4.3cm/s versus 8.8 $\pm$ 2.6cm/s, p = 0,047) but not in the posteromedial region (10.3 $\pm$ 3.6cm/s versus 8.6 $\pm$ 2.6cm/s, p = 0.24).

Conclusions: Bicuspid aortic valve causes higher hemodynamic stress in the anterolateral region of the ascending aorta than tricuspid aortic valve.

VALVE PROTHESES

P3052 Time course of the prosthetic valve function after aortic valve replacement with tilting-disc mechanical valves

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Most of the previous investigations on the outcome of the prosthetic valve have focused on the clinical events. This study was designed to investigate the time course of the mechanical valve functions after aortic valve replacement and the influence of the intensity of the anticoagulation on them.

Methods: This study included 115 patients who underwent aortic valve replacement with Medtronic-Hall valves and had no history of prosthetic valve thrombosis (64 males, mean age: 58±9.1y.o.). The sizes of the valves were 21 mm in 50 patients, 23 mm in 52 patients, and 25 mm in 13 patients. Valve resistance (R) (dynes sec cm^{-5}) and peak transprosthetic gradient (PG) (mmHg) were estimated by transthoracic echocardiography every year. The patients were divided into 2 treatment groups based on the mode of PTINR values measured during follow up: more intensive treatment group (the mode>2.3) and less intensive treatment group (the mode<2.3).

Result: The mean follow up period was 53±39 months. R and PG showed time-dependent increases in 21 mm and 23 mm valve patients (R: 6.3/year, 2.4/year, respectively; PG: 1.5/year, 1.2/year, respectively). In 21 mm valve patients, R and PG showed more time-dependent increases in less intensive treatment group than in more intensive treatment group (R: 7.8/year vs. 5.5/year, p = 0.0002; PG: 1.9/year vs. 1.3/year, p = 0.0002). However, there was no difference between 2 groups in 23 mm, 25 mm valve patients.

Conclusion: The tilting-disc mechanical valve functions showed time-dependent deterioration in smaller valves. Additionally, in smallest valve, less intensive anticoagulation might progress its deterioration.

P3053 The influence of mechanical valve noise on quality of life results from the ESCAT study

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Objective: The "Early Self Controlled Anticoagulation Trial" (ESCAT) was conducted to evaluate the thromboembolic and hemorrhagic complications, other aspects of patient outcomes were also studied. This report analyzes data related to quality of life impairment due to the sound made by different mechanical prostheses.

Methods: A total of 1255 patients who received one of three different valves (St. Jude, CarboMedics, Medtronic Hall) were included in this study. Patients were asked "Have you recently felt impaired by heart valve noise?" as part of the ESCAT protocol and were additionally asked to complete the SF-36 quality of life questionnaire. The SF-36 was used to evaluate patients' perceptions of their physical and psychological well-being to see if these criteria were related to patients' perceptions of valve noise. Descriptive statistics (mean, sd) were used to summarize continuous data and percentages were used to summarize categorical data. Analyses of variance and covariance were calculated in accordance with the general linear model.

Results: The majority of patients felt they were not significantly impaired by valve noise. The number who felt significantly impaired at six months (10.6%) fell to 5.7% by 24 months. The perception of valve noise and the change in this perception over time were not related to valve type, valve position or the number of valves implanted (p>0.05). Evaluation of gender differences indicated an increased perception of valve noise by female patients (p=0.0001), especially those in younger age groups. This difference remained significant throughout the follow-up period. The results of the SF-36 questionnaire indicate that patients who feel less able to work, less able to function in their role, more pain and a lower perception of general physical health are also more likely to be moderately or very disturbed by the noise of their valve. Furthermore, a marked relationship with the psychological subscales of the SF-36 was also shown.

Conclusion: Based on the results of this study, we conclude that patients' perceptions of being impaired by the noise of their prosthetic valves might be predicted by four factors: female gender, young age, impairment of social contacts and a negative perception of one's own state of health. Contrary to previous beliefs, valve type, valve position and the number of valves implanted were not predictors of valve noise impairment.

P3054 Treatment with erythropoietin for severe haemolytic anemia caused by small periprosthetic leaks

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Background: Severe hemolytic anemia due to small periprosthetic leaks is an indication for a surgical refixation or re-replacement of the prosthesis. We report about three patients, who previously had three or more cardiac operations and in whom a decompensated hemolytic anemia was recompensated by chronic treatment with erythropoietin (EPO) and a high-risk reoperation could be avoided.

Patients: . Patient A (male, born 1941) had St. Jude Medical (SJM) valve replacement for severe aortic regurgitation and reoperation for prosthetic valve endocarditis caused by S. aureus in 1988 with re-re-operation for severe periprosthetic dehiscence four months later. 10 months later he developed a decompensated hemolytic anemia (lactat dehydrogenase [LDH] 1140 U/l, hemoglobin [Hb] 8.7 g/dl) due to a small periprosthetic leak. Hb could be stabilized (12.2 g/dl) with a weekly dosage of 25.000 IE EPO, while LDH still amounts to 1100 U/l.

Patient B (female, born 1933) had open mitral commissurotomies in 1963 and 1978, and combined mitral and aortic valve replacement with Björk Shiley (BS) prostheses in 1983. The mitral prosthesis had to be re-replaced in 1997 (Carbomedics M30) for prosthetic valve dysfunction due to tissue ingrowth. 5 months postoperatively severe hemolytic anemia (LDH 980 U/l, Hb 9.5 g/dl) due to a small periprosthetic leak occurred and could be stabilized by 20.000 IE EPO/week at a Hb of 11.6-12.5 g/dl.

Patient C (male, born 1955) had aortic surgery for coarctation in 1972, aortic and mitral valve replacement (BS) during acute infective endocarditis in 1982, emergency re-re-operation (SJM-M31) for strut fracture of the BS mitral prosthesis in 1990. In 1999 refixation of the mitral prosthesis because of a small and aortic valve re-replacement (SJM-A25) because of a large periprosthetic leakage was mandatory. 5 months later he developed severe hemolysis (Hb 9.2 g/dl, LDH 1170 U/l) due to a small periprosthetic leak of the aortic prosthesis. With 30.000 IE EPO/week the hemolysis was compensated (Hb 12.4 g/dl, LDH 1040 U/l).

Conclusion: Erythropoietin may recompensate severe hemolytic anemia in patients with hemodynamically insignificant periprosthetic leaks, so that a high-risk reoperation may be postponed or even avoided.

P3055 Are mechanical valves with enhanced inner diameter advantageous in the small sized aortic annulus?

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Background: Mechanical bileaflet valves with enhanced inner diameter may offer superior hemodynamic properties in patients with a small aortic annulus. The aim of this study was to compare these valves with standard prostheses in vivo.

Methods: Mechanical aortic valve replacement for combined stenosis and insufficiency was performed in 48 patients with standard CarboMedics prostheses (CM: 21mm, 23mm, 25mm) and two types of diameter enhanced St. Jude Medical prostheses (SJMAHPJ: 21mm, 23mm, 25mm; SJMRegent: 21mm, 23mm). Intraoperatively, transvalvular mean gradients (TVG) were assessed by means of transesophageal echocardiography (TEE) and by means of simultaneously assessed direct pressure monitoring of the left ventricle and the ascending aorta (CATH) after weaning from cardiopulmonary bypass at 100beats/min constant heart rate (sinus rhythm or atrial pacing).

Results: In all valves and sizes both TVG assessments exhibited consistent findings although TEE assessment appeared to overestimate TVG moderately. Small sized conventional valves of 21mm showed a marked initial TVG while both valve types with enhanced inner diameter exhibited significantly lower TVG. These differences disappeared in larger sized valves.

Transvalvular Gradients

(n=6)	TVG (CATH)	TVG (TEE)
CM 21mm	15.6±3.9*	22.6±4.1*
CM 23mm	7.8±0.8	10.3±1.0
CM 25mm	9.2±2.2	10.9±1.9
SJMAHPJ 21mm	11.9+.1.6	14.4±1.6
SJMAHPJ 23mm	7.7±1.4	9.3±1.1
SJMAHPJ 25mm	8.2±1.1	10.7±1.7
SJMRegent 21mm	9.9±1.1	11.5±1.7
SJMRegent 23mm	9.5±1.8	11.8±1.9

*=p<0.05 CM 21mm vs. SJMAHPJ 21mm, SJMRegent 21mm

Conclusion: In patients with a small aortic annulus, who require a 21mm valve, diameter enhanced prostheses should be implanted in order to provide adequately low gradients. Proper left ventricular remodelling in the intermediate course can then be expected.

P3056 Native and prosthetic aortic valve endocarditis: replacement with new Stentless valves

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The valve substitute of choice in aortic valve endocarditis with annulus abscess is the cryopreserved homograft. The Shelhigh™ No-React® stentless (SNRS) valves and conduits were considered as an alternative when no suitable homograft was available

Methods: From January 2000 to October 2001, 76 SNRS valves and conduits were implanted in patients with native/prosthetic endocarditis at the Deutsches Herzzentrum Berlin. In 41 consecutive patients (study group) suffering from the most severe form of endocarditis, including aortic ring abscess in 27 (68%), urgent aortic valve replacement with the SuperStentless® valves and stentless aortic valve conduit was undertaken (size 21 to 27 mm, mean 23.2). The control group consists of 68 patients with abscess in whom an aortic homograft was implanted for endocarditis with ring abscess. There were no significant differences between the two groups in incidence of epinephrine use, heart failure and demographic data preoperatively.

Results: Sixty-day mortality was 16% (11 patients) for the control group (homografts), compared with 7% (three patients) in the study group. Re-infection occurred in 4% (three patients) in the control group and in 2% (one patient) in the study group. Mean EOA for the stentless valve was 2.3 ± 0.6 cm^2, which is an optimal value. Postoperative echocardiographic LVEDD differed significantly ($p < 0.05$) for the study group compared with controls (46 ± 8 mm vs. 56 ± 9 mm), whereas LVEF and mean cw-Doppler gradient did not (56 ± 18% vs. 53 ± 17% resp. 11 ± 5 mmHg vs. 12 ± 6 mmHg).

Conclusions: Our early experience with No-React® stentless valves and conduits in patients with aortic native/prosthetic ring abscess demonstrates good results similar to those of cryopreserved homografts.

COMPUTER DEMONSTRATION

3197 Morphology of ST depression during isolated subendocardial ischaemia: computer simulation and clinical validation

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We have developed a software capable of deriving surface ECG patterns based on endocardial and epicardial action potential curves simulating intact versus ischemic myocytes. We observed that during simulated unambiguous subendocardial ischemia the morphology of ST-segment depression (STD) is essentially " horizontal" and that unnatural changes of the endocardial action potential curve are needed to obtain a downsloping pattern of STD. To define the morphologic STD pattern ("horizontal" or "downsloping"?) associated with "isolated" subendocardial ischemia, we performed a clinical validation of our computer simulation. Methods: From a series of consecutive patients (pts) with high pre-test probability of coronary artery disease and displaying STD in leads V3-V4 during exercise stress test (EST), two groups were selected: I, 25 consecutive pts (19 males, age 60 + 8 years) with horizontal STD (>1mm), becoming downsloping into the recovery; II: 16 consecutive pts (11 males, age 61±7 years) with a horizontal pattern also into the recovery ("only horizontal"). Pts underwent coronary angiography within 10 days from EST. A luminal diameter of > 50% was considered significant coronary stenosis. We considered the presence of isolated anterior subendocardial ischemia when V3-V4 STD was observed in association with an isolated left anterior descending (LAD) lesion. In presence of right coronary artery (RCA) or circumflex (Cx) lesions and normal LAD, the V3-V4 STD was considered a reciprocal ECG change manifestation of an inferior/ posterior-lateral wall transmural ischemia. A combination of anterior subendocardial ischemia and inferior posterior transmural ischemia could be present when both LAD and RCA/Cx lesions co-existed. Results: Group I pts showed significant coronary lesions in the Cx (in I pt), in the RCA/ Cx (in 4 pts) and in the LAD, RCA/Cx (in 20 pts). Group II showed isolated LAD lesion in 15 pts. One patient had normal coronaries. Group I pts demonstrated more severe angiographic coronary lesions both in terms of number (I= 2.5 ± 0.5 vs II= 1.1 ± 0.5 vessels, $p < 0.0001$) and severity of vessels involved (I=94 ± 6 vs II= 82 + 7%, < 0.0001). Conclusions: in our pts, V3-V4 STD during "isolated" subendocardial ischemia appeared to be of the "only horizontal" type. A downsloping morphology of V3-V4 STD appeared to be associated with EST inducible TMI in the opposite wall, supplied by severely stenotic branches of the Cx and/or RCA, with or without concomitant LAD lesions. Our computer model accurately predicted the observed clinical results.

3198 Is accurate non-invasive imaging of the human atrial activation sequence feasible?

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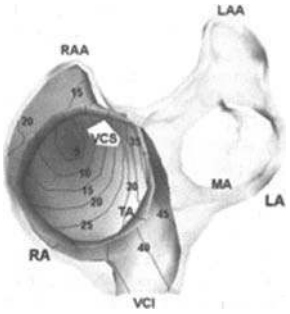
Non-invasive determination of the focal origin of atrial arrhythmias may be important for catheter ablative treatment of atrial fibrillation. The aim of our study was to reconstruct human atrial activation (AT) maps, using 65-lead body surface mapping (BSM) and MRI.

Methods: MRI scanning (torso: 10 mm slice thickness; atrium: cine mode, short axis, 4 mm) was performed in 4 patients (2f, age 33±9) without structural heart disease. Following ablation of supraventricular arrhythmias, BSM and electroanatomic CARTOTM mapping was performed: Right atrium (RA), during sinus rhythm (SR, N=3) and coronary sinus ostium pacing (CS, N=1); and left atrium (LA, N=1, SR and CS). After 3D anatomic reconstruction, using MRI data, AT maps were estimated for the respective atrium. The reconstructed AT patterns were validated with the CARTO TM maps.

Results: Figure: Anatomical reconstruction of both atria. Color-coded AT map of the RA during SR (dark - earliest activation; isochronal lines with numbers in ms; MA=mitral annulus; LAA/RAA= RA/LA appendage; VCI/VCS=inferior/superior vena cava; TA=tricuspid annulus). The mean geometric error between CARTOTM maps and the atrial model was 5.3 ±1 mm, the localization accuracy of the first endocardial breakthrough was 11±6 mm. Sufficient qualitative correlation with the CARTOTM maps was found.



Conclusion: Our findings demonstrate that noninvasive imaging of the atrial activation sequence with a high spatio-temporal resolution is feasible in man. Further studies for quantitative validation in patients with clinical focal arrhythmias are necessary.

Day 5

Wednesday 4 September 2002

PULMONARY VEIN ISOLATION IN ARTIFICIAL FIBRILLATION

3213 Clinical and electrophysiologic predictors of pulmonary vein stenosis following radiofrequency catheter ablation for atrial fibrillation

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Background: Radiofrequency catheter ablation (RFCA) has been used for treating atrial fibrillation (AF). However, pulmonary vein (PV) stenosis is still an important limitation. The predictors of PV stenosis are not well established.
Methods: To determine predictors of PV stenosis as a consequence of RFCA, we studied 139 patients presenting with refractory paroxysmal or persistent AF. 333 PVs were ablated in 158 procedures (126 RSPV (37.8%), 97 LSPV (29.1%), 81 LIPV (24.3%), and 29 RIPV (8.8%). PV stenosis was defined as greater than 50% narrowing of the PV, according to baseline measurements by contrast-enhanced spiral CT scanning. The following variable were evaluated: gender, age, type of AF, duration of AF, presence of structural cardiac disease, LVEF, left atrial size, PV ablated, number of burns, maximal temperature of ablation, total energy applied, baseline PV diameter at the orifice and 1-2 cm into the vessel. The data were analyzed using t-test or Fisher's exact test as appropriate.
Results: Of a total of 333 PV ablated, PV stenosis was observed in 20 (5.9%) veins (6/126 RSPV, 5/97 LSPV, 8/81 LIPV, and 1/29 RIPV). There was no difference in clinical features between patients with and without PV stenosis, including age, duration of AF, left atrial size, and LVEF. The mean energy applied was higher in pt with PV stenosis (31±1.3 KJ vs. 21±3.9 KJ, p=0.017). There was no difference in highest temperature reached and number of burns in patients with and without PV stenosis (23±12 vs. 19±12, p=0.14). The mean PV orifice at baseline was smaller among pt with acquired PV stenosis 18±6 mm vs. 24±7 mm, 0=0.003). The number of PVs with a diameter of 15 mm or less at baseline was significantly higher in PV stenosis patients (25% vs. 8.1%, p=0.03, OR: 3.8, 95% CI: 1.2; 12.1).
Conclusions: In this study, ablation of the LIPV, the amount of energy applied, and the baseline size of PV was correlated to PV stenosis after RFCA for treatment of AF. These data could be helpful in avoiding PV stenosis.

3214 Correlating the pathology and physiology of long-term block in circumferential pulmonary vein ablations

W.W. Su, S.B. Johnson, L. Leite, D.L. Packer on behalf of Mayo Clinic. *Rochester, United States of America*

Background: Circumferential ablation at the pulmonary vein (PV) orifice for the treatment of atrial fibrillation has had limited success, which maybe due to difficulties in creating continuous and full-thickness lesions. In theory, small discontinuities may occur without jeopardizing block, since muscle fibers are not continuous around the PV orifice. However, the correlation between pathology and successful electrical block is unclear.
Methods: To assess the impact of any discontinuity within a circumferential lesion on long-term block, 38 PV lesions were created in 18 dogs, which were then survived to either 4 or 6 months. Circumferential ablation using a laser-energy balloon catheter was performed at 3.5 to 5.5 W/cm. End-points were either successful acute bi-directional electrical isolation or a cumulative energy delivery time of 600 seconds. Entrance and exit block were reassessed at the end of the survival period. Post-mortem examination of the gross and histological specimens was performed to categorize the circumferential PV discontinuities in terms 12 clock-face sectors.
Results: Of the 38 PVs ablated, chronic entrance and bi-directional block was confirmed in 9 PVs (24%). Of these, 6 PVs (5 RSPV and 1 LSPV) had 100% circumferential lesion around the PV orifice, and 3 PVs (all LSPV) contained < 8% gaps, located at the inferior aspect of the PV. Of the 29/38 PVs without long-term block, 15/29 PVs had initial acute block: RSPV in 8 with 30±24% discontinuities inferiorly, and LSPV in 7 with 32%±27% discontinuities inferiorly. In the remaining 13/29 PVs, acute block was never achieved: RSPV in 3 with 29±11% gap inferiorly; LSPV in 6 with 29±10% gap inferiorly; LIPV in 5 with 58±45% gap inferiorly.
Conclusions: Excellent correlation exists between the pathology of pulmonary vein ablation and the physiology of long-term block. Chronic bi-directional block of the PV usually requires complete circumferential ablation, although small gaps do not preclude successful disconnection. Most discontinuities greater than 8% will preclude long-term block in the canine heart.

3215 Distinguishing left superior pulmonary vein potentials from left atrial far field activity

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Elimination of distal pulmonary venous muscle activity is considered necessary to treat atrial fibrillation by catheter therapy. However, inspite of extensive proximal ablation, potentials may persist particularly in the left pulmonary superior veins (LSPV).
Methods: 35 patients with PAF (29 M, 56±11 yrs) were studied. A Lasso decapolar circular catheter was placed within the LSPV and RF ablation performed at electrophysiologically defined proximal inputs into the vein. Recordings were obtained from the Lasso 10 to 15 mm inside the LSPV and from the left atrial appendage (LAA) during sinus rhythm, distal and proximal coronary sinus as well as left atrial appendage pacing. Angiography of the LAA was performed in at least 2 different radiographic projections to view the 10 Lasso electrodes en face and their anatomic relationship to the LAA.
Results: Before ablation, pacing from the coronary sinus or LAA separated single sinus rhythm LSPV electrograms into two components linked by continuous electrograms at the input(s) into the vein. LAA pacing produced greater separation compared to distal, while proximal CS pacing resulted in least separation (98±29 vs 83±30 vs 55±30ms, $p<0.05$)The first component was synchronous with LA appendage activity, while the second was sharper with a proximal to distal sequence of activation in the vein. LAA stimulation captured this component with a very short activation time or made it disappear by incorporation within the stimulation artifact. After proximal ablation the first component was still recorded either limited to anterior Lasso bipoles or recorded in all but with the greatest amplitude and sharpness in anterior electrodes within the LSPV.This consistently corresponded to the position of the nearest atrial structure demonstrated by angiography to be the left atrial appendage.
Conclusion: A fusion potential composed of LA appendage and venous muscle activity is recorded in sinus rhythm within the LSPV. Therefore even after successful PV ablation, residual potentials recorded within the left superior pulmonary vein emanate from the left atrial appendage and should not be the target of continued ablation.

3216 Discordance of post ablation exit and entrance block from circumferential pulmonary vein energy deliveries

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Background: Electrical isolation of the pulmonary vein (PV) is crucial in treating atrial fibrillation originating within the vessel. In most clinical settings, entrance block is used as the end point to assess the efficacy of PV ablation. This presupposes that entrance block equates to exit block.
Method: To verify the concordance between entrance and exit block after circumferential ablation of PV ostium, 32 PVs were ablated in 20 dogs with a circumferential laser energy balloon catheter. 3.5 watt/cm^2 to 5.4 watt/cm^2 (average= 4.3 watt/cm^2) energy was delivered for 120 to 600 seconds (average= 225 seconds). Pre and post ablation study of entrance and exit block was assessed in each PV using a multi-polar catheter positioned across the PV sleeve. Entrance block was assessed during normal sinus rhythm and pacing from the coronary sinus, with exit block assessed during pacing from the distal PV sleeve.
Results: Absence of intra-PV potentials with NSR and distal coronary sinus pacing (entrance block) was seen in 26 of 32 PVs (81%). Exit block determination was confounded by incomplete PV capture after ablation. Nevertheless, with local capture, block was seen in 17 of 32 PVs (53%) Reversal of orifice level activation at the line of block was seen in 2 of 32 PVs. Discordance of entrance and exit block was noted in 9 of the PVs (28%) after the ablation, for which 8 of the PVs had only entrance block, and 1 PV showed exit without entrance block. Concordant bi-directional block was present in 18 of 32 PVs (56%). Similarly, concordant absence of entrance and exit block was present in 6 of 32 PVs (19%).
Conclusion: Exit and entrance block after PV ablation is frequently discordant. Therefore, entrance block after PV ablation is an inadequate surrogate endpoint for cure. This may be important in explaining recurrent AF in clinical cases using entrance block as the indicator for completion.

3217 Adenosin induces pulmonary vein activity after successful ostial pulmonary vein isolation: evidence for a "new pathway"

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Arrhythmogenic triggers originating from the pulmonary veins (PV) have been identified as cause for paroxysmal atrial fibrillation (AF) in selected patients (Pts). Currently, radiofrequency (RF) catheter ablation of the PV ostium with resulting pulmonary vein isolation offers a potential for cure in these pts. We studied the effects of isoproterenol (ISO) and adenosine (ADO) on PV activation after successful ostial PV isolation.

Methods: We studied 19 pts (mean age 53±8 years, 11 male) with refractory highly symptomatic persistent (n=8), or paroxysmal (n=11) AF. PV isolation was performed utilizing RF catheter ablation technology during left atrial to pulmonary vein activation mapping in sinus rhythm guided by a LASSO- (CORDIS) or multipolar BASKET-catheter (EPT). After successful PV isolation we studied the effects of intravenous ISO (0.2-0.3 mg) and intravenous ADO (12-18 mg) on activation of the upper PVs during CS pacing.

Results: A total of 48 PV were successfully isolated. Intravenous ISO had no effect on PV activity. After ADO, PV activity could be recorded in 9 of 19 left upper PV studied coupled to the atrial activity. This pulmonary vein activation was documented as lasting an average of 21 ± 11 seconds. In 6 of these 9 cases the PV activation was from distal to proximal. No effect of ADO was seen on PV activity in the right upper PV.

Conclusions: ADO induces PV activity in the left but not the right upper PV following successful ostial PV isolation procedure. The distal to proximal activation sequence suggests a possible PV activation via the ligament of Marshall. The pathophysiological role of this "pathway" is not yet known.

3218 Pulmonary veins ostia electrical disconnection and anatomical pulmonary veins isolation: two sides of the same treatment?

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There are currently two radiofrequency (RF) ablation techniques for percutaneous electrical isolation of pulmonary veins (PV): circumferential isolation and electrical disconnection of the PV ostia.

In order to assess how different these techniques are, we evaluated how close do contiguous RF lesions need to be to achieve electrical disconnection.

Population and methods: We studied 26 PV, in 9 patients with paroxysmal atrial fibrillation who underwent PV mapping and RF ablation. To map the PV ostia we used a circumferential 10-electrode catheter (Lasso™) and a Navistar™ catheter for precise anatomical definition of PV ostia and for RF ablation. After assessment of circumferential distribution and activation sequence of PV potentials, atrial ablation (near PV ostia) was performed at segments showing earliest activation to obtain PV electrical disconnection. Each RF application aimed at <50°C, output<30W and duration<30 seconds.With electroanatomical mapping we measured the PV ostia diameter and the RF maximal circumferential distance between contiguous RF applications.

Results: 26 PV were mapped (6 left superior, 6 left inferior, 9 right superior and 5 right inferior). To obtain PV electrical disconnection, RF energy was applied following the activation sequence. In some areas several applications were needed, and in others few or no applications were performed. A larger PV ostium diameter was associated with the need for a superior number of applications (r=0.51; p=0.008). However, no relation was found between PV ostium diameter and the maximal distance between contiguous RF applications (r=0.13; p=ns). Considering an expected radius of the RF lesion of 2.5 mm, the mean distance between lesion areas was thus inferior to 5 mm (see table).

	RF applications number (mean±SD)	PV ostium diameter mm (mean±SD)	Maximal distance between RF appl. mm (mean±SD), range
LSPV	14.5±2.7	15.1±2.2	9.3±3.0 (5.9 to 14.0)
LIPV	13.5±4.5	13.5±1.8	9.1±1.5 (7.3 to 11.6)
RSPV	23.8±9.4	16.5±2.6	8.1±1.6 (6.4 to 11.1)
RIPV	12.8±5.3	12.8±2.6	9.9±1.2 (8.8 to 12.0)

Conclusions: The density of the RF applications performed on the PV ostium was heterogeneously distributed over the ostium's perimeter. The electrical disconnection endpoint was only achieved after an almost circumferential RF lesion was created.

NEW TRENDS IN IMAGING

3219 3D reconstruction of coronary arteries using intravascular ultrasound and biplane x-ray projections and its quantitative validation

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The aim of the present study was the validation of a novel method for three dimensional reconstruction of coronary arteries.

Methods: We assessed the accuracy of: I) the catheter path reconstruction, II) the relative axial twist of IVUS frames, III) the absolute orientation of IVUS frames, IV) our automated contour detection algorithm for IVUS images. The accuracy of catheter path reconstruction was tested using a metal wire with 11 radiopaque markers, attached at 15mm intervals. The wire was bent in helical turn. The reconstructed wires length and the intervals of radiopaque markers were compared with the real values. For the determination of the relative axial twist of IVUS images, a gutter was machined in helical course on the surface of a plastic cylinder. The gutter was closed by a flat strip. In this way gutter cross-sections had a flat side aligned to the cylinder surface. The validation of our algorithm was achieved by comparing the 3D reconstructed gutter with the original. However, to establish the accuracy of our algorithm in real vessels and determine the accuracy of absolute frame orientation, the coronary arteries of 3 cadaveric pig heart were reconstructed using metal clips for markers. The validation of absolute frame orientation and the angular rotation of IVUS frames was based on the comparison of the 3d reconstructed peak of IVUS stamps with the reconstructed metal clips. Image registration technique was used for the evaluation of the segmentation algorithm for the identification of luminal and media/adventitia borders in IVUS images. For this propose, 64 frames from 8 patients were used for manual determination of the regions of interest by two expert observers and the results were compared with the outcome of the automated segmentation algorithm. Correlation coefficient, slope, y interception, regression analysis, WI, inter – and intra – observer variability were applied so as to determine the reliability of our algorithm.

Results: The results include inter-observer variability less than 3%, intra-observer variability less than 2% for the examination of arteries segments from different patients. Details also are given for the absolute orientation of IVUS frames as it is computed by experimental data.

Conclusion: By the proposed validation method we are able to determine the reliability of each step, which was made for the 3D reconstruction of the coronary arteries and to estimate the accuracy of our 3D reconstruction algorithm.

3220 Angiographic data compression: a comparison of different methods

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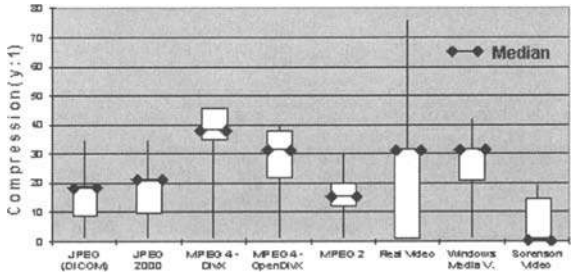
Background: Compression of angiographic data offers easy storage and fast transmission over narrow band networks. We evaluated the image quality of various compression schemes.
Methods: A set of 10 coronary angiogramms was compressed with 8 different methods: Joint Photographic Experts Group (JPEG), JPEG 2000, Moving Picture Experts Group (MPEG) in MPEG-4 from DivX, MPEG-4 from Open DivX, MPEG-2, Real® Video, Windows® Media Video and Sorenson® Video. A team of 10 experienced cardiologists (mean of 3954 examinations each) reviewed the angiogramms. The 80 angiogramms were presented in a randomized, databased sequence with 6 different compression factors and the original for comparison (total data set of 490 films). The examiner selected in each of the 80 series the image quality he judged adaquate for diagnostic purpose.
Results: The median of tolerable compression for diagnostic purposes was for JPEG 19:1, for JPEG 2000 21:1, for MPEG-4 (DivX) 38:1, for MPEG-4 (Open DivX) 31:1, for MPEG-2 15:1, for Real® Video 32:1, for Windows® Media Video 32:1 and for Sorenson® Video at 1:1. The table shows the boxplot.



Comparison of compression methods.

Conclusion: The Digital Imaging and Communications in Medicine (DICOM) protocol uses the single image compression of JPEG and JPEG 2000, which allows a moderate compression ratio. The film compressor MPEG-2 shows no advantage. The proprietary formats of Real® Video, Windows® Media Video and Sorenson® Video revealed wide changes in acceptable compression ratio. The international MPEG-4 standard offers the best compression ratio regarding image quality and seems suitable for large archives and telemedicine applications.

3221 Better angiographic images at lower Xray dose with an integrated flat panel detector

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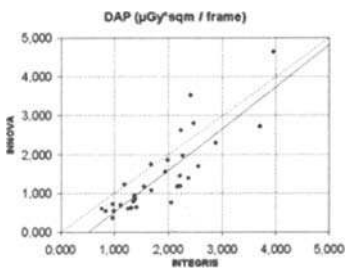
Recently integrated flat panel detectors (FPD) have become available for angiocardiography with enhanced image content quality due to a better signal-to-noise ratio and enlarged gray level resolution (12 to 14 bit) as compared to conventional image intensifier/digitized video systems (8 bit), which renders possible advanced image processing techniques (DRM) leading to a picture quality so far unseen. We have reported previously on static phantom studies that have yielded better flat panel image resolution for fluoroscopy as well as cine-like aquisition (2.3 to 2.5 lp/mm for 12cm through 20cm fields of view (FOV)) as compared to contemporary conventional (CON) equipment (<2 lp/mm for all FOV >14cm). Despite this increase in resolution, Xray doses were consistently lower for FPD than CON at identical gantry positions.
Since it is unclear whether these data can be extrapolated to the situation of clinical coronary angiography (CA), we have compared image quality and measured Xray dose-area-product per frame (DAP/fr) in patients who had coronary stent implantation in our institution. CA was performed with CON (Integris H 5000, Philips) and FPD equipment (Innova, GE) at identical FOV and gantry settings for 32 paired assessments in 4 different views.



Average DAP/fr was 1,837 µGy m^2 for CON vs 1,423 µGy m^2 for FPD ($p < 0.001$). The distribution and regression line of paired DAP measurements is given in the graphic. Stent strut visibility and stent structure recognition was significantly better in all FPD runs.
In conclusion, FPD imaging allows for improved image quality with at least comparable, if not lower X-ray dose during clinical coronary arteriography.

3222 Application of neuronal network for tissue identification of intracardiac masses in adults

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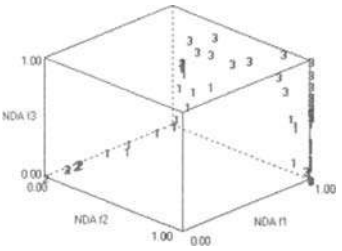
Aim: Intracardiac masses differ in their echocardiographic appearance although the visual recognition of their histological classification remains a challenge. We aimed to evaluate the feasibility of neuronal network-based approach for the computer-based identification of tumors.
Methods: 108 images from echocardiograms of patients with masses classified as thrombi (62 images), benign neoplastic (31) and malignant neoplastic (15) were digitized and analyzed with custom software. For each image, a region of interest covering a representative section of the image was defined and 254 image features were calculated (including 9 from pixel histogram, 6 from gradient matrix, 20 from Run length matrix and 220 from 2nd order histogram). 10 most efficient parameters were selected using classification error minimalization approach. Linear and non-linear (neuronal network) discriminative analysis was used in the same dataset.
Results: Simple analysis based on pixel feature histograms was insufficient for mass classification. Analysis based on 3 best parameters was 52% successful and linear discriminative analysis still classified correctly only 55% of images. Neuronal network approach allowed correct classification of 91% (10/108, $p<0.0001$). Graph shows distribution of classes in nonlinear discriminative analysis.



Conclusions: Simple parameters of tissue texture derived from echocardiogram are insufficient for the discrimination of intracardiac thrombi, benign and malignant neoplasms. However, the use of neural network allows correct classification of >90% images in our preliminary series. Validation of this approach in broader dataset is required to create a framework for digital expert systems supporting qualitative echocardiographic diagnosis of intracardiac masses.

3223 Proximal arbitrary surface conservative assessment of leakage (PASCAL): a new Echo-Doppler method for quantification of mitral regurgitation

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Background: The proximal isovelocity surface area (PISA) method used for quantification of mitral regurgitation is based on the assumption that the isovelocity contours proximal to the regurgitant orifice are hemispherical, however in the complex flow fields of the heart this assumption is limited. In addition, the two-dimensional color Doppler display, while able to provide detailed information regarding the instantaneous velocity of flow parallel to the Doppler scan direction, is unable to represent the orthogonal components of flow velocities. We developed a new approach for quantification of mitral regurgitant flow [proximal arbitrary surface conservative assessment of leakage (PASCAL)] based on physical principles and mathematical handling of echocardiographic images of flow convergence. This approach has been described in this study, tested using a mathematical model, validated with an in vitro study, and finally applied in patients with mitral regurgitation.
Methods and Results: A color Doppler image of a mitral regurgitant flow at peak systole was transformed into a numerical matrix of the axial component of the velocity. The velocity vector was evaluated by the condition of incompressibility integrating the continuity equation, then the instantaneous flow rate was computed by application of the control volume method. Finally, determination of peak velocity and time velocity integral by continuous wave Doppler allowed calculation of the total regurgitant volume. Numerical simulation demonstrated that regurgitant flow rate evaluated by PASCAL is independent of the selected value of radius, whereas PISA method underestimates the real value for small radius and overestimates for large radius. Experiments with an in vitro model demonstrated the high accuracy of PASCAL (error 0.26%). Finally, application on patients with mitral regurgitation confirmed the feasibility and consistency of PASCAL, with a relative error <7%.
Conclusions: A rigorous application of the fluid dynamic laws to color Doppler images allows a non-invasive quantification of mitral regurgitation which is independent of geometric assumption.

CATHETER ABLATION IN ATRIAL FIBRILLATION – LINEAR LESIONS

3228 Are contineous linear lesions associated with ablation success in patients with chronic atrial fibrillation

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A catheter-based, left atrial (LA) ablation procedure was performed using non-contact mapping (NCM) in 14 patients (pts) with chronic atrial fibrillation (CAF). The LA lesion geometry used has been shown to be effective in pts with CAF, in whom intraoperative RF-catheter ablation was performed to eliminate anatomically defined "anchor" reentrant circuits. Aim of this study was 1) to translate a successful surgical LA intervention into a catheter procedure, 2) to evaluate the usefulness of NCM to identify and close discontinuities in linear lesions, 3) to assess the impact of linear lesion continuity on ablation success of CAF.
Methods: LA-ablation was performed with four linear lesions between the mitral annulus and the left inferior pulmonary vein (PV), to the left upper PV, then to the right upper PV, and finally to the right lower PV in 14 pts with CAF. During online analysis, NCM revealed conduction across gaps in the linear lesions in all pts (overall 58 gaps were found with a mean of 4.5 ± 0.9 gaps/pts). In addition contact mapping was performed. With contact mapping a discontinuity of linear lesion was identified by a localized loss of double potentials in 27 of the 58 gaps (47%). In the remaining 31 gaps (53%) interpretation of contact mapping was difficult because of the diminished amplitude of local electrograms. Catheter ablation was guided by NCM until complete conduction block was observed. During follow-up of 12 ± 7 months, 6/14 pts (43%) remained in sinus rhythm without antiarrhythmic drugs (in 5 of the 6 pts no gap was identified during offline analysis) and an additional 4 pts were maintained in sinus rhythm with antiarrhythmic drugs (in all 4 pts 1 gap was identified during offline analysis), resulting in an overall success rate of 71% (10/14 pts).
Conclusions: The intraoperative radiofrequency ablation strategy could be translated into a catheter based procedure using NCM. the overall success rate was 43% without and 71% with additional antiarrhythmic drugs. All pts without gaps during offline analysis were free of recurrence. All pts with a recurrence of CAF had more than 1 gap identified after the initial ablation procedure. Successful ablation of CAF is associated with continuity of linear lesions.

3229 Modification of the atrial substrate by left atrial linear lesions in symptomatic patients after pulmonary vein isolation

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Trigger elimination by pulmonary vein (PV) isolation has been proposed to cure drug-refractory atrial fibrillation (AF) with varying success. Despite initially successful PV isolation, atrial fibrillation may re-occur during follow-up. Reasons for arrhythmia recurrence might include re-conduction or new atrial triggers.
Methods: Of an initial cohort of 158 pts (36 f, mean age 56 ± 10 years) that underwent pulmonary vein isolation (125 pts with intermittent AF), 38 pts a second ablation attempt was performed because of arrhythmia recurrence during follow-up. After repeat transseptal puncture, a repeat interruption of a conducting fibre was performed, if a spike potential could be recorded (max. 30 W, 50° C over max 180 sec). Again, the loss of PV spike was demonstrated at the end of the procedure. Because of ineffectiveness of this approach to ascertain stable sinus rhythm, a total of 5 pts (4 male, mean age 52 ± 12 years) underwent an ablation procedure aiming at a compartmentalization of the left atrium by two linear lesions: one connecting the superior right to the superior left PV ("roof" line) and a second one from the middle of the roof line to the anterior aspect of the mitral annulus. Mapping and ablation was performed with the assistance of the electroanatomical mapping system CARTO (and an irrigated 4 mm ablation electrode in 4/5 pts) during constant right atrial or coronary sinus pacing.
Results: A mean number of 46 ± 23 RF applications were used to deploy the two linear lesion. Procedure duration amounted to a mean of 489 ± 81 min and 21.8 ± 5.4 min of fluoroscopy. Validation of linear lesion completeness was performed using both conventional stimulation techniques and the features of the CARTO system.
During follow-up (median of 113 days), 4/5 pts are in stable SR without the need for antiarrhythmic medication.
Conclusion: Relapse of the arrhythmia after demonstrated complete pulmonary vein isolation might be caused by re-conduction of the previously interrupted conducting fibres into the pulmonary vein. However, even after repeat "successful" pulmonary vein isolation, atrial fibrillation does reoccur in a subset of patients. Modification of the left atrial substrate by long linear lesions offers a further option to finally ascertain sinus rhythm.

3230 Linear epicardial radiofrequency catheter ablation in patients with refractory atrial fibrillation

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It has been reported that creating a line of block connecting the four pulmonary veins to the mitral annulus during cardiac surgery, prevents sustained atrial fibrillation (Afib) in around 80% of the patients with permanent Afib. Transthoracic epicardial mapping is a method to directly achieve the pericardial space allowing ablation catheters to be inserted inside the oblique sinus against the pulmonary veins. The aim of this study was to evaluate the feasibility of creating epicardial linear lesions to treat patients with refractory Afib in the electrophysiology laboratory. Patients: Seven patients (46.1±9.5, all men) presenting refractory atrial fibrillation, five paroxysmal and two permanent (6 and 12 months) were referred for epicardial catheter ablation. All patients except one (mitral valve disease) presented normal heart. Patients with paroxysmal Afib had been submitted to at least two procedures before, for RF focal ablation or pulmonary vein isolation. Methods: An octapolar catheter (6-mm length electrodes) was inserted, under anesthesia, in the pericardial space through transthoracic pericardial puncture for linear ablation. A 4-mm regular catheter was also inserted in the left atrial through the transeptal approach to explore the endocardial signal during and after the epicardial ablation. We tried to make either two lines of block along the pulmonary veins towards the mitral annulus or to connect the four PV to the mitral annulus. Results: It was possible to place the epicardial catheter in the oblique sinus, close to the pulmonary veins in all patients. Two lines connecting pulmonary veins to the mitral annulus were obtained in three patients. One line connecting right or left PV to the mitral annulus was obtained in four patients. An important electrogram amplitude reduction (>80%) was recorded by both epicardial and endocardial sites in most lines. When the signal amplitude was still high after epicardial RF pulse, we applied RF through the endocardial catheter. During follow-up (3-15 months), three patients remained in stable sinus rhythm (one of them presented one reversible episode of atrial flutter). Conclusion: Pericardial approach is a feasible method to create RF linear lesions in the left atrium to treat patients with refractory atrial fibrillation.

3231 Linear lesions or linear lesion plus pulmonary vein isolation: a comparative study using intraoperative ablation of atrial fibrillation

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Intraoperative radiofrequency ablation of atrial fibrillation by substrate modification with the induction of contiguous left atrial lesion lines has been shown to be highly effective. It is currently unclear whether additional trigger elimination by pulmonary vein isolation adds treatment efficiency. Thus, two different treatment strategies of intraoperative ablation of atrial fibrillation were compared in 30 consecutive patients (pts.; 26 men, 4 women, mean age 53 ± 8 yrs.) undergoing the procedure with minimal invasive surgery: In group one (grp. I, 15 pts.) linear lesions were deployed in the left atrium between the mitral annulus and the pulmonary veins while in group two (grp. II, 15 pts.) linear lesions (same as grp I) and complete isolation of all pulmonary veins was performed. There were no differences in the incidence of paroxysmal (60%) and permanent AF (40%) between both groups. All pts. underwent surgery exclusively for the treatment of AF.
Results: Treatment time for intraoperative induction of linear lesions was 17 ± 6 minutes and treatment time for induction of linear lesions plus pulmonary vein isolation was 24 ± 7 minutes ($p < 0.05$) At discharge, sinus rhythm was present in 91% of pts. in both groups. In 5 pts. of both groups, electrical cardioversion was necessary following surgery. The use of antiarrhythmic drugs (flecainide or amiodarone) in the early postoperative period was moderately lower in grp. II pts. (47% versus 66%; p = n.s.).
The results of this comparative study indicate that pulmonary vein isolation in addition to substrate modification with linear lesions does not significantly add treatment efficiency. Thus, the induction of linear lesions seems to be sufficient to cure both, pts. with paroxysmal and chronic AF.

3232 Right-sided ablation in selected patients with paroxysmal atrial fibrillation: a multicenter prospective study

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Controversy still exists regarding the true clinical benefit of right atrial linear ablation in paroxysmal atrial fibrillation (AF). A multicenter study was designed to prospectively investigate the clinical outcome of a selected population with highly symptomatic drug-refractory AF undergoing right-sided radiofrequency ablation. Lack of the typical clinical scenario suggesting focal origin of AF (i.e. occurrence of frequent premature atrial contractions preceding AF onset) along with disorganized right atrial activity at mapping, constituted the main criteria for choosing the right sided approach. Seventy-two patients (pts) (38 males, mean age 58 ±8 years) were enrolled in the study and received three ablation lines by using a 6 pole, 7F ablation catheter (Amazr, Medtronic, Inc.). Systemic hypertension was detected in 33 pts (46%), ischemic heart disease in 4 pts (6%) and no organic heart disease in 34 pts (46%). Procedural time was 105±48 minutes and X-ray exposure 32±18 minutes. No procedure related complications occurred. After ablation, antiarrhythmic drug treatment was unchanged in 58 pts (81%) while the remaining 14 pts (19%) were off-drug. Three categories (Class 0= failure; Class 1= >50% AF reduction; Class 2= >75% AF reduction) identified the clinical outcome over a mean follow up of 268±119 days as expressed in Table 1. Overall data shows that Class 0 included 10 pts (15%); Class 1 18 pts (25%)and Class 2 44 pts (60%). Semiquantitative evaluation of quality of life showed significant clinical improvement in 78% of pts.

	A (9 pts)	B (5 pts)	C (22 pts)	D (36 pts)
Follow up	< 90 days	90-180 days	180-270 days	> 270 days
Class 0	0	0	3 (14%)	7 (19%)
Class 1	4 (44%)	1 (20%)	4 (18%)	9/25%)
Class 2	5 (56%)	4 (80%)	15 (68%)	20 (56%)

Class 0= failure; Class 1= >50% AF reduction; Class 2= > 75% AF reduction.

Conclusions: In a selected patient population, creation of right linear ablation with antiarrhythmic drugs can affect the atrial substrate of AF promoting over the follow-up improvement of quality of life by markedly reducing or abolishing the clinical episodes of the arrhythmia.

3233 Prevention of paroxysmal atrial fibrillation in patients affected by sinus bradycardia: role of right atrium linear ablation and pacing site

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Background: Interatrial septal (IAS) pacing has been proposed for paroxysmal atrial fibrillation (PAF) prevention in pts with sinus bradycardia (SB). Recent studies have shown the role of atrium compartmentalization obtained by RF right atrium linear lesions (RALL) in treating PAF pts.
Aim: 1) Determine if the IAS pacing is more effective than non septal sites (NSS) pacing in reducing PAF burden. 2) Evaluate if RALL supplies additional benefits to atrial pacing.
Methods: 52 pts (26 M, mean age 72±11 years) with SB and PAF (at least 2 symptomatic episodes in the last year) were implanted with the Medtronic AT500TM pacemaker (PM). At implantation, patients were randomized to be treated by PM only (26 pts) or PM plus RALL (26 pts). Pacing site was also randomized (29 IAS pts and 23 NSS pts). RF ablation was performed using 3-D mapping (Carto system) along two lines: 1) from superior vena cava (VC) to inferior VC; 2) between inferior VC and tricuspid anulus. PM diagnostics allowed to measure PAF burden (hours/day). Antiarrhythmic therapy was maintained stable after implant.
Results: All pts were followed for at least 7 months. The first post-implant month was not considered in data analysis. PAF burden, expressed as mean±st.dev, was significantly ($P<0.05$) higher: 1) in NSS pts 2.3±5.9 than in IAS pts 0.2±1.1; 2) in NSS-RALL pts 3.1±6.7 than in IAS-RALL pts 0.3±1.4; 3) in NSS-no RALL pts 0.9±3.2 than in IAS-no RALL pts 0.1±0.7.
Conclusions: 1) in pts with SB and PAF IAS pacing is more effective than NSS pacing in preventing PAF; 2) pts who underwent RALL had no additional benefit from this procedure

DIABETES AND CARDIOVASCULAR DISEASE

3247 Intensive insulin treatment reduces transient ischaemic episodes during acute coronary events in diabetic patients

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Aim: This study tested the impact of intensive metabolic treatment with insulin on transient myocardial ischaemia detected with continuous 12-lead ST segment monitoring during non-ST segment elevation acute coronary syndromes in type 2 diabetic patients.
Methods: The study included 57 type 2 diabetic patients with non-ST segment elevation acute coronary syndromes. Twenty-eight patients randomized to conventional treatment plus intensive insulin therapy (Group A) and twenty-nine to conventional therapy only (Group B). Group A patients received insulin by infusion for 48 hours according to a predefined protocol aiming to maintain normoglycaemia. Group B patients were treated according to coronary care unit usual care. The ST segment monitoring was performed for 48 hours in the coronary care unit. The two groups were comparable in terms of medical history, clinical, and biochemical data.
Results: Three patients from both groups were excluded from the analysis because there was objective evidence for evolution in ST segment elevation acute myocardial infarction. Six patients (24%) from Group A vs. twelve from Group B (46.2%) had evidence of transient ischaemia ($p=0.098$). Group A patients showed significantly lower values in the median number [Group A vs. Group B: 1(range: 1-3) vs. 3.5 (range: 2-14), $p<0.01$] and total duration of ST-episodes [Group A vs. Group B: 10 (range: 3-20) min vs. 37.5 (range: 10-100) min, $p<0.01$]. Multivariate analysis revealed that the mean plasma glucose during the study period was powerful predictor of the presence (b: 0.377, $p<0.01$), the number (b: 0.523, $p<0.001$) and the total duration (b: 0.686, $p<0.001$) of ST-episodes respectively.
Conclusions: Intensive insulin treatment considerably decreases the number and the total duration of ST-episodes in type 2 diabetic patients suffering from non-ST segment elevation acute coronary syndromes.

3248 Acarbose reduces incidence of type 2 diabetes and of myocardial infarction in subjects with impaired glucose tolerance: The STOP-NIDDM trial

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Impaired glucose tolerance (IGT) is a high risk category for type 2 diabetes and cardiovascular morbidity. Atherosclerosis starts before type 2 diabetes (T2DM) is diagnosed. In multivariate analysis postprandial (pp) hyperglycemia was found to be a significant predictor of both development of T2DM and its comorbidities. Acarbose (A), an a-glucosidase inhibitor by its unique mode of action reduces pp hyperglycemia.
The STOP-NIDDM trial therefore investigated the effect of A on the prevention of T2DM and cardiovascular disease in middle aged subjects with IGT. The study was an international multicentre double-blind, placebo-controlled randomised trial. IGT-subjects (n = 1,429) were randomised to either placebo or A 100 mg 3 times a day for a mean follow-up time of 3.3 years. Both males (50.5%) and females (49.7%) participated with a mean age of 54.5 + 7.9 years and a mean BMI of 30.9 + 4.2 kg/m^2. The primary end-point was the development of diabetes based on an oral glucose tolerance test done yearly. Secondary outcomes included the development of hypertension and cardiovascular disease. Sixty-one (61) subjects (4%) were excluded; they did not have IGT or had no post-randomisation data leaving 1,368 subjects for intent-to-treat analysis. Twenty-three (23) percent (n = 341), discontinued prematurely, 211 in the A-treated group and 130 in the placebo group, these subjects were also followed for outcome parameters. A total of 221 (32.4%) subjects randomised to acarbose treatment and 285 (41.5%) randomised to placebo treatment developed diabetes. Using the Cox proportional hazard model, acarbose reduced the risk of diabetes by 25% [relative hazard = 0.75 (95% CI = 0.63-0.90); p = 0.0015]. Furthermore, the study medication also resulted in a significant increase in the reversion of IGT to normal glucose tolerance (NGT) ($p < 0.0001$). A. was also effective in reducing the occurrence of myocardial infarction: relative hazard = 0.08 (95%CI = 0.01-0.59); P = 0.0138]. It furthermore significantly reduced the incidence of newly diagnosed hypertension. This outcome speakes in favour of our working hypothesis that A by control of pp hyperglycemia protects the b-cells of the pancreas from glucotoxity as well as the endothelium from noxious effects of pp glucose spikes.
In conclusion, acarbose treatment delays the conversion of IGT to T2DM and increases the reversion to normal glucose tolerance. It also significantly decreases the incidence of myocardial infarction and hypertension in this high risk population.

3249 Significantly higher mortality in patients with IDDM compared to patients with NIDDM and non-diabetics undergoing coronary interventions

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Background: Previous studies have demonstrated a significant difference in outcomes between diabetics and nondiabetics undergoing percutaneous coronary interventions (PCI). Differences in outcome between IDDM and NIDDM have not been studied.
Methods: Study samples consisted of 18,309 consecutive PCI performed between July 1997 and February 2001 in a consortium of 8 hospitals. Of the 18,309 patients who underwent PCI, 4,856 were diabetics. In the diabetic cohort, 1,772 had IDDM and 3,084 patients had NIDDM. Clinical, procedural, and outcome data were collected prospectively by use of a standardized data collection form.
Results: Mortality in patients with IDDM undergoing PCI was significantly higher compared to patients with NIDDM and no diabetes (Table 1). There were no significant differences in MI, stroke and emergent CABG rates between groups. The composite endpoint of death/MI/stroke/CABG was significantly higher in patients with IDDM driven by mortality. After adjustment for demographics and comorbidities there was a strong trend towards worse survival in IDDM with the adjusted odds ratio of death for IDDM vs no-DM of 1.41 (95% CI: 0.95-2.09, P=0.08) and for NIDDM vs no-DM of 1.21 (95% CI: 0.84-1.73, P=0.31).
Conclusions: There is significant heterogeneity in outcomes including mortality between patients with IDDM and NIDDM after PCI. Patients with IDDM have higher mortality after PCI compared to NIDDM. Patients with IDDM should be aggressively targeted for risk factor modification and should be the focus of further clinical research to improve outcomes.

Table 1

	IDDM (n=1772)	NIDDM (n=3084)	No DM (n=13453)	P
Death	3.05%	1.75%	1.46%	0.003
MI	2.48%	2.14%	2.10%	0.44
Stroke	0.34%	0.32%	0.39%	0.93
Emergent CABG	0.96%	0.71%	0.79%	0.36
Death/MI/Stroke/CABG	6.43%	4.28%	4.30%	0.001

Clinical outcomes in diabetics and nondiabetics undergoing percutaneous coronary interventions. Diabetics are stratified by insulin dependent (IDDM) and non insulin dependent (NIDDM)P value is for outcomes between IDDM and NIDDM patients.

3250 One-year outcome of high-risk patients with acute myocardial infarction with or without diabetes: data from the MISTRAL study

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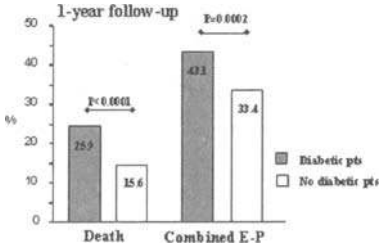
Background: Pts with diabetes (D) have more often severe and complicated coronary arteriosclerosis with high risk (HR) of acute myocardial infarction (AMI) and cardiac death. We studied in-hospital and 1-year outcomes of HR pts with AMI with or without D treated with reperfusion therapy (thrombolysis or primary-PCI) or drug therapy.
Methods and results: 2227 HR-pts with ST-elevation AMI <12 h were recruited at 17 centres with, and 30 without, feasibility of performing primary PCI (classified at HR having ≥>1 of the following characteristics: female >70 y, diabetic >70 y, Killip class >1, SBP <100 mmHg and heart rate >100 b/m, >4 leads with ST deviation, previous Q-wave AMI, contraindication to thrombolysis [10.2%]). 1795 pts (80.6%) had not D and 432 pts (19.4%) were diabetic: pts with D were more frequent females, older, presented more often with a history of cardiovascular disease, bradi and tachi-arrythmias during hospital stay and heart failure at entry. Pts with D were less treated with reperfusion therapy (74.3% vs 83.0%, p<0.0001) and with betablockers at discharge (41.2% vs 49.5%, p<0.005).
One year mortality rate and combined end-point (death + reinfarction + heart failure + angina) are reported in the figure. When we adjusted the 1-year outcomes for all clinical, haemodynamic variables and therapy, D still remained an independent prognostic predictor (death *OR* 1.54 95%CI 1.13-2.09; combined end-point OR 1.13 95%CI 0.89-1.43).



Conclusion: This study confirms, in a large unselected cohort of HR-pts with AMI, that D is a significant independent predictor of poor prognosis. Neverthless, pts with D are often undertreated with aggressive mechanical or pharmacological therapy.

3251 Exercise and mortality among men with diabetes in the Physicians' Health Study enrollment cohort

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Purpose: Diabetics have at least a 2-3 fold increased risk in overall mortality compared to non-diabetics. Vigorous exercise reduces risk of CVD by 20 to 50% in the general population. We therefore sought to examine the association between exercise and mortality among diabetics.
Methods: The Physicians' Health Study (PHS) is a randomized, double-blind, placebo controlled trial of low-dose aspirin and beta carotene in primary prevention of CVD and cancer. We conducted a prospective cohort study of the 2838 U.S men from the enrollment cohort between the ages of 40-84 years old in 1982 with reported diabetes and without history of MI, stroke or cancer. Assessment of physical activity was estimated by self-reported frequency of vigorous exercise enough to work up a sweat on the enrollment questionnaire. We used Cox proportional hazards regression to analyze the data.
Results: There were 356 deaths over the 5.2 years of follow-up. We observed an inverse linear relationship between frequency of exercise and total mortality. With adjustment for age, smoking, alcohol intake, and history of angina and/or transient ischemic attack, the relative risk of death from all causes for those who exercised 1-3 times/month, 1 time/week, 2-4 times/week, > 5 times/week compared to those who rarely or never exercised were 0.73 (95% confidence interval [CI], 0.50 to 1.05), 0.66 (95% CI, 0.47 to 0.93), 0.57 (95% CI, 0.42 to 0.76), and 0.45(95% CI, 0.31 to 0.66) respectively. When we additionally controlled for body mass index, history of hypertension and high cholesterol, corresponding relative risks were 0.70 (95% CI, 0.47 to 1.05), 0.73 (95% CI, 0.51 to 1.03), 0.58 (95% CI, 0.43 to 0.79), and 0.49(95% CI, 0.33 to 0.73) respectively. The P value for trend was <0.0001 in both multivariate models.
Conclusions: Exercise is associated with a significant reduction in overall mortality among men with diabetes and no history of MI, stroke, or cancer. The association is linear with increasing relative risk reduction through to the highest exercise category. The effect persists when controlled for age, and other mortality associated risk factors. The effect appears to be in part independent of exercise's effect on BMI, hypertension and cholesterol.

3252 Predictors of outcome in diabetic patients after successful percutaneous coronary interventions

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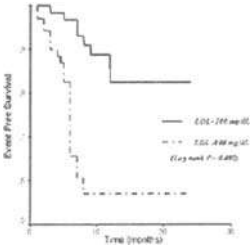
Background: Diabetic patients have a worse outcome after percutaneous coronary interventions (PCI). We sought whether long-term outcome of diabetic patients after successful PCI is influenced by: 1) vascular complications, 2) HbA1c levels, and 3) plasma cholesterol levels, at the time of revascularization.
Methods: From January to July 2001, 150 consecutive diabetics underwent successful PCI at our Institution. Differences in: a) clinical, angiographic and procedural variables, b) HbA1c >7%, c) presence of retinopathy, d) creatinine, microalbuminuria and cholesterol levels, were assessed in patients with (n= 40, Group A) and without (n= 110, Group B) major cardiac events (MACE, i.e. myocardial infarction, death, bypass surgery, re-PCI)at follow-up (10±4 months).
Results: The main angiographic and procedural characteristics were similar in the 2 groups. Stent was implanted in 84% of patients (82% in Group A and 85% in Group B, p= 0.66). IIb/IIIa antagonists were used in 29.5% of patients (28% of Group A and 30% of Group B (p= 0.79). Microalbuminuria >20 mg/24h occurred in 23% of patients in Group A vs. 25% in Group B, p= 0.53). HbA1c >7% (37.5% vs. 16%, p=0.007), retinopathy (50% vs. 23%, p= 0.01), chronic renal insufficiency (26% VS. 12%, P=0.033), and higher cholesterol levels (total 208±51 vs. 183±39 mg/dl, p= 0.005; LDL 124±38 vs. 102±33 mg/dl, p= 0.001) were more frequent in Group A. By stepwise logistic regression analysis, predictors of MACE were LDL (RR= 1.02; 95% CI= 1.01-1.04; p= 0.019; figure), HbA1c (RR= 4.45; 95% CI= 1.33-10.26; p= 0.012), and chronic renal insufficiency (RR= 3.93; 95% CI= 1.16-13.32; p= 0.028).



Conclusions: The degree of metabolic (both lipidic and glycemic) control may influence long-term outcome after successful PCI in diabetic patients.

VASCULAR STRUCTURE AND FUNCTION

3253 Progesterone attenuates the beneficial effects of hormone replacement therapy on large artery elasticity in hypertensive postmenopausal women

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Nowadays, based on the results of HERS study, the cardiovascular beneficial effects of hormonal replacement therapy (HRT) on postmenopausal women are in doubt. Whether there are differential effects of combined and uncombined HRT on large artery stiffness, a well-recognized risk factor for cardiovascular outcome, has not been well defined.

Methods: Towards this end, we studied aortic compliance in 56 postmenopausal women (age 52±5 years, 3.4±1 years after menopause) with untreated, mild essential hypertension randomized to either conjugated estrogen alone (n=20), estrogen plus medroxyprogesterone (n=20) or placebo (n=16). Aortic elasticity was evaluated non-invasively on the basis of pulse wave velocity (PWV) measurements at baseline and at 12 weeks after treatment.

Results: In our women BMI was 27±4 Kgr/m^2, office BP 146/93 mmHg, left ventricular mass index (LVMI) 104±26 gr/m^2, and plasma levels of total cholesterol 230±21mg/d. The three groups were matched regarding age, time since menopause, smoking status, office BP, BMI, LVMI and PWV values at baseline. At 12 weeks of treatment, in the women receiving estrogen alone, aortic PWV was significantly reduced (231±17 vs 209±15 cm/sec, p<0.005), while in the women receiving combined HRT or placebo, PWV did not change (232±20 vs 228±18 and 233±14 vs 230±16 cm/sec, respectively, p=NS for both cases). In all three groups, BP and heart rate values did not change significantly after treatment. At baseline, aortic PWV had a positive correlation with womens' age (r=0.32, p<0.05) and LVMI (r=0.29, p<0.05).

Conclusions: Long-term combined HRT is without beneficial effects on large artery function in hypertensive postmenopausal women. These findings supports the view that progesterone may attenuate the beneficial effects of unopposed HRT.

3254 ETA receptors mediate vasoconstriction whereas ETB receptors clear endothelin-1 in the splanchnic and renal circulation of healthy men

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Background: The study was undertaken to investigate the contribution of endothelin (ET)A and ETB receptors to basal vascular tone and ET-1-induced vasoconstriction in the renal and splanchnic vascular beds of healthy humans.

Methods: ET-1 (4 pmol x kg-1 x min-1 i.v.) was infused alone, in combination with the selective ETA receptor antagonist BQ123 (5 nmol x kg-1 x min-1) or the selective ETB receptor antagonist BQ788 (4 nmol x kg-1 x min-1) in six healthy men. Renal and splanchnic blood flows were determined by para-amino hippuric acid and cardiogreen clearance, respectively.

Results: Administration of ET-1 evoked increase in arterial blood pressure and renal as well as splancnic vascular resistance. BQ123 did not affect basal arterial blood pressure, splanchnic or renal vascular resistance. However, BQ123 greatly reduced the increase in splanchnic and renal vascular resistance induced by ET-1 (58±13 vs. 11±12%; P<0.05 and 36±6 vs. 12±3%; P<0.0001 respectively). BQ788 significantly increased basal splanchnic and renal vascular resistance (38±16%; P=0.01 and 21±5%; P<0.0001 respectively), and potentiated the increase in renal vascular resistance in response to ET-1 (67±14 vs. 36±6%; P<0.01). Plasma levels of ET-1 increased significantly more in the presence of ETB receptor blockade than under control conditions and in the presence of ETA receptor blockade.

Conclusion: These findings suggest that ETA receptors play a more important role in mediating vasoconstriction in the splanchnic and renal vasculature than ETB receptors in healthy humans in vivo. The ETB receptor seems to exert a clearance function which may modulate vascular tone by altering the plasma concentration of ET-1.

3255 Intra-brachial Aldosterone does not acutely alter forearm vascular resistance in healthy male volunteers

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Background: Systemic infusions of aldosterone cause an acute increase in systemic vascular resistance (SVR) in healthy subjects. It is not clear whether this is due to local vascular effects or is a consequence of the previously reported effects on baroreflex function. We investigated the non-genomic short-term effects of locally infused aldosterone on the forearm resistance bed.

Methods: We studied 9 healthy male volunteers (age 31±3.8) on an ad libitum diet (24-hour urinary Na excretion 137.8±19.7mmol). Following a baseline 0.9% saline infusion for 6 minutes, Aldosterone was administered into the brachial artery at 0.5ml/min at doses of 20, 100, and 200ng/ml incrementally for 10 minutes each. At baseline and at the end of each infusion, forearm blood flow (FBF) was measured simultaneously using strain gauge plethysmography, in both the infused and the non-infused contralateral arms. Arterial blood pressure was continuously recorded using finger photo-plethysmography. Forearm Vascular Resistance (FVR) was calculated from the flow-pressure data. Venous effluent blood from both arms was analysed for plasma levels of aldosterone at baseline and at the end of each infusion. Changes in forearm blood flow and forearm vascular resistance in the infused arm were corrected for those occurring in the non-infused arm.

Results: Plasma aldosterone levels increased in a dose dependent fashion in venous blood of the infused arm (from 113.3pg/ml at baseline to 1230.6pg/ml at peak infusion rate, p<0.001) but did not change in the non-infused arm. In the infused arm Aldosterone had no effect on absolute FBF (2.62mls/100ml forearm volume at peak infusion Vs 2.68mls/100ml forearm volume at baseline p=NS) or absolute FVR (32mmHg/ml per 100ml forearm volume at peak infusion Vs 30mmHg/ml per 100ml forearm volume at baseline p=NS). Corrected for changes in the control arm, FBF increased by 4.1% (p=NS) and FVR by 4.3%(p=NS) at peak infusion.

Conclusions: Local intra-arterial infusion of aldosterone, sufficient to raise plasma levels to those seen in severe congestive cardiac failure had no acute, non-genomic effect in the forearm resistance bed in healthy male volunteers.

3256 An ultrasound-based method for determining pulse-wave velocity in the carotid artery

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Background: The pulse wave velocity (PWV) is related to arterial stiffness and determines the timing of the reflected wave. It can be estimated from arterial cross-sectional area and brachial pulse pressure by the Bramwell-Hill (BH) method. The aim of this study was to present and evaluate a non-invasive alternative to the BH method.

Method: It can be shown from wave propagation theory that PWV equals the ratio between arterial flow and cross-sectional area during reflection-free periods of the cardiac cycle. PWV can therefore be estimated as the slope of the straight portion of the area-flow (AQ) loop (Fig. 1, left panel, thick line). In two anaesthetized dogs and 21 human subjects (age 23-74) we measured the carotid flow and cross-sectional area non-invasively by ultrasound (Fig. 1, right panel).

Results: As predicted by the pressure dependency of arterial stiffness, the estimated PWV decreased when the aortic pressure was lowered in the two dogs. In the human subjects, the AQ and BH estimates were correlated (r = 0.44, p < 0.05). The difference was -0.14 ± 1.12 m/s (mean ± SD). When the human subjects were divided into three age groups (<35 years, 35-55 years and >55 years), both methods gave group means that increased with age (AQ: 5.62, 5.85, and 6.52 m/s, respectively. BH: 5.29, 6.29 and 6.86 m/s, respectively). For the BH method, the youngest group was significantly different from the middle and oldest age groups (p < 0.05). For the AQ method, the groups of the youngest and oldest tended to be different (p = 0.13).

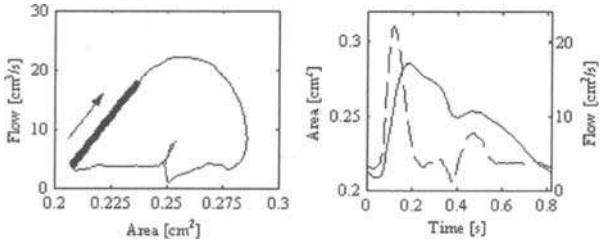

Fig 1: Area (solid) and flow (dashed).

Conclusion: We derived a new method for estimating PWV that can be based solely on ultrasound measurements of cross-sectional area and flow. Hence, the use of brachial pulse pressures is avoided.

3257 Endothelial dysfunction and coronary vasospasm in essential hypertensives with normal coronary arteries

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Background: The possible relationship between coronary endothelial dysfunction and susceptibility to coronary vasospasm has not been investigated in patients with essential hypertension (EH).
Methods: To this purpose we studied 24 EH patients (mean age with 57±8 yrs, 10 males, mean pressure 109±15 mmHg) with angiographically normal coronary arteries. Coronary flow velocity was continuously measured by Doppler catheter in the proximal LAD together with coronary pressure from the guiding catheter. After baseline measurements (Bas), the protocol included acetylcholine (Ach) (15 mcg/min and 45 mcg/min)and adenosine (Ado) (1mg/min) infusions. Quantitative coronary angiography was scheduled at the end of each step. Coronary Flow (CF) was calculated as coronary flow velocity times coronary cross sectional area.
Results: In all patients Ado infusion could be performed, while only 18 patients completed the Ach protocol. In 6 patients transient coronary vasospasm occurred during the second Ach infusion, associated with chest pain in all and ST segment elevation in 4. In these patients CF measured at the end of the first Ach infusion was used for further analysis. CF changes during Ach were heterogeneous in the whole population. According to the median value of max % CF increase during Ach, patients were divided into two groups, with higher (Group 1) or lower (group 2) CF response, respectively. The % CF change (mean±SE) was higher in Group 1 than in Group 2 either during Ach 15 mcg/min (42.8±16.2 vs minus 14.1±12.3, $p<0.05$) or Ach 45 mcg/min (138.6±37.7 vs 0.6±6.9, $p<0.01$). By contrast, the % CF increase during Ado was not different between the two groups (239±31.9 vs 166±25.8, ns). Spasm occurred in 1/12 pts of Group 1 and in 5/12 pts of Group 2.
Conclusions: In pts with essential hypertension coronary flow response to acetylcholine is heterogeneous and not related to adenosine dependent vasodilating capability. A blunted response to acetylcholine is associated with higher likelihood of coronary vasospasm. These data suggest that coronary endothelial dysfunction is associated with increased vasomotor reactivity in hypertension.

3258 Soluble CD14 influences aortic stiffness but not brachial blood pressure in a population-based study

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Objectives: Soluble CD14 (sCD14), an effective mediator for the activation of monocytes by bacterial endotoxin is involved in the release of substances able to modify the characteristics of the arterial wall. Also, in endotoxin-injected spontaneous hypertensive rats, the duration of delayed hypotensive phase was lower than in WKY rats: this is associated with an attenuated inflammatory response. The aim of the study was to investigate in humans the role of sCD14 on brachial blood pressure (BP) and on aortic stiffness.
Population and methods: A population sample of 905 healthy subjects aged 35-64 years randomly selected from the electoral rolls were recruited between 1995 and 1997 by the Toulouse MONICA centre. After fasting, blood sample was drawn and a questionnaire was administered. Heart rate, BP and carotid femoral pulse wave velocity (PWV) were successively measured in supine position. Carotid-femoral PWV was measured using a semi-automatic device (Complior). Common carotid intima media thickness (IMT) and the presence of plaques were assessed by ultrasonography. sCD14 was measured using an immuno enzymatic method (IBL, GmbH, Hamburg, Germany).
Results: In bivariate analysis, PWV, IMT, the presence of plaques and systolic BP (SBP) were positively associated with sCD14 ($p<0.01$) whereas no significant relationship was observed between sCD14 and diastolic BP. After adjustment for age and sex, no significant relationship remained between IMT, the presence of plaques, SBP and sCD14. A significant and positive relationship ($p<0.05$) was observed between PWV and sCD14 after adjustment for age, sex, heart rate, SBP and insulinemia.
Conclusion: This cross-sectional population-based study yields first evidence that sCD14 strongly influences aortic stiffness independently of age, BP and atherosclerosis.

NEW ASPECTS OF NEUROHORMONAL REGULATION IN HYPERTENSION

3259 Atrial muscarinic M2 receptor down-regulation by insulin in adult rat atrial cardiomyocytes: a link between obesity and hypertension?

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Introduction: Mechanisms leading to hypertension in patient with hyperinsulinism (i.e. diabetes or obesity) remain to be defined. In an experimental model of obesity-related hypertension and hyperinsulinism (high-fat diet in dogs) we previously reported a decreased density of M2- cholinoceptors (M2-R) in right atrium. We sought to assess, in vitro, the influence of insulin (I), on M2 muscarinic receptivity in isolated atrial cardiomyocytes issued from adult rat(AC).
Methods: AC were isolated and cultured in the presence or in absence of increasing concentrations of insulin (10^{-12} to 10^{-6} M) for 24 hours. Ligand binding assay using [3H]N-methylscopolamine (a non-specific M2-R antagonist) on intact cells was performed to determine M2-R number and Kd. The expression level of mRNA encoding M2 receptors in controls and treated cells was measured using semi-quantitative RT-PCR analysis using mRNA encoding GAPDH as an internal control.
Results: Insulin induced a dose- and time-dependent down-regulation of M2R. The density of M2-R decreased from 286±45 fmoles/105 cells to 178±32 fmoles/105 cells ($p<0.005$) without any modification of Kd. In the same way, insulin induced a dose-dependent decrease of the ratio M2/GAPDH. These transcriptional modifications are time- and concentration-dependent and were detected after 24 hours of incubation. The ability of carbachol to inhibit the increase in cAMP production induced by forskolin was not modified by incubation of cells in the presence of insuline (10-6M).
Conclusion: These data suggest a role of insulin on atrial M2-R expression. This regulation might be explained by a genic effect involving a Mitogen Activated Protein kinase pathway (data not shown). Our results provide insight about the effect of insulin on the heart and the possible role of this hormon in the genesis of hypertension and arrhythmias (i.e. decreased heart rate variability thus increased risk of sudden) in patient with hyperinsulinism(diabetes or obesity).

3260 Validation of a novel technique to eliminate breathing influence from basic RR interval signals

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Introduction: Power spectral analysis of RR interval variability is an established technique to investigate the autonomic nervous system. However, power spectra are strongly influenced by respiratory patterns. Until recently, only mathematical adjustments for this confounding factor could be made. We hypothesised that when using frequency-filtering techniques from speech technology, basic RR interval signals can reliably be filtered from respiratory influences.
Methods: In 26 healthy drug-naive subjects (mean age 40 ± 11 y, 13 M/13F, age matched), 5-min recordings of RR interval were made in the supine position. Two 'baseline' recordings were obtained after 30 min of supine rest as well as two during metronomic breathing (slow, 6/min and fast, 15/min) to serve as quality control. RR interval was computed from peripheral continuous ECG leads while breathing pattern was concomitantly assessed using a nasal thermistor. Recordings were separated by a 5 minute rest.
Results: Power spectral indices (auto-regressive method) had a Gaussian distribution and are given in normalised units (NU). Low (LF, ~0.1 Hz) and high (HF, ~0.25 Hz) frequency components in the basic signals were 0.41 ± 0.12 NU (mean ± SD) and 0.59 ± 0.12 NU respectively, resulting in a ratio of 0.763 ± 0.370. After correcting the basic signals from respiratory influence, this yielded LF and HF of both 0.50 ± 0.09 NU and a ratio of 1.043 ± 0.334 (all $p<0.001$). During slow metronomic breathing, we observed a LF peak of 0.64 ± 0.05 NU and a HF peak of 0.36 ± 0.05 NU, resulting in a ratio of 1.836 ± 0.333. After adjustment, we obtained LF and HF peaks of both 0.50 ± 0.07 NU with a ratio of 1.033 ± 0.284 ($p < 0.001$). During fast metronomic breathing, LF and HF peaks were respectively 0.33 ± 0.13 NU and 0.67 ± 0.13 NU, which yields a ratio of 0.551 ± 0.326. Adjustment for breathing transformed both LF and HF to 0.50 ± 0.08 NU, resulting in a ratio of 1.027 ± 0.301 ($p < 0.001$). There was no statistically significant difference between the adjusted values of the baseline and the metronomic breathing spectral indices.
Conclusion: Basic RR-interval signals can be reliably filtered from confounding respiratory influences.

3261 Association of β1-adrenergic receptor polymorphism with blood pressure and left ventricular mass in a population study

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An arginine (Arg) to glicine (Gly) substitution at aminoacid position 389 of beta1-adrenergic receptor is characterized by higher levels of basal and isoproterenol stimulated adenylyl cyclase activity in cell cultures. In addition, preliminary data from a case-control study suggest that individuals homozygous for the Arg389 allele are at increased risk to develop hypertension.
To examine the effect of the b1-AR Arg/Gly389 polymorphism on blood pressure and cardiac structure and function in a sample of general population.
Five-hundred and sixty subjects (aged 35 to 64) were enrolled in the study. They were randomly selected from the electoral rolls of a small town of approximately 8.000. Clinic and 24-hour ambulatory blood pressure (ABPM), as well as indexes of left ventricular (LV) structure and function (echocardiography) were obtained in each subject. Beta1-AR Arg/Gly389 polymorphism was characterized by PCR-restriction typing.
Blood pressure was significantly higher in Arg389 homozygotes both at clinic and 24-hours measurements. Differences were similar for systolic and diastolic blood pressure and for day-time and night-time measurements. The relative risk of hypertension for Arg389 homozygotes was 1.26 (1.03-1.55, CI 95%). Heart rate differences were not statistically significant. Interventricular septum and posterior wall thickness, as well as calculated LV mass were higher in Arg/Arg389 individuals. Echocardiographic indexes of LV systolic and diastolic function (ejection fraction, fractional shortening, Ev/Av) did not differ significantly between genotypes.

	Arg/Arg389 (n=279)	Arg/Gly389 + Gly/Gly389 (n=281)	ANOVA
Clinic SBP/DBP, mmHg	137.3/84.4 ±1.15/0.60	133.2/82.6 ±0.95/0.56	p = 0.006/ p = 0.027
ABPM SBP/DBP, mmHg	122.9/78 ± 0.70/0.49	121.0/76.5 ±0.71/0.51	p = 0.057/ p = 0.044
Left ventricular mass index, g/m^2	90.5±1.76	84.8±1.51	p = 0.014
SBP Adjusted LVMI	89.3±1.60	84.8±1.59	p = 0.049

Homozygosis for beta1-AR Arg389 allele is associated to slightly but significantly higher blood pressure and to increased risk of hypertension. Arg389 is also associated to increased LV mass and this relationship seems not only attributable to blood pressure differences but possibly also to increased cardiac adrenergic stimulation.

3262 Transforming growth factor-beta1 levels in hypertensive patients: association with body mass index and leptin

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Transforming Growth Factor-b1 (TGF-b1) is a multifunctional growth factor/cytokine that has been suggested to be overexpressed in hypertension. A relationship between obesity and hypertension is well known, and leptin, an adipocyte-specific ob gene product, has been shown to play a role in obesity-related hypertension. Since previous in vitro studies demonstrated a biological interaction between leptin and TGF-b1, the aim of this study was to evaluate a possible in vivo association between TGF-b1, body mass index (BMI) and leptin circulating levels in hypertensive subjects.
The study was conducted in 29 consecutive normal weight, 29 overweight and 46 obese hypertensive patients. To study the effect of weight loss, twenty of the hypertensive obese patients (11 women, 9 men, BMI 35.6±6, mean age 37±13 y) were fed a diet providing 1300kcal/day. Metabolic, anthropometric and biochemical parameters were evaluated at the baseline and after weight loss. Plasma TGF-b1 and leptin levels were measured by using a specific ELISA in accordance with the manufacturer's instructions. Peripheral blood mononuclear cells of healthy subjects were separated by Ficoll-Hypaque gradient and seeded into Petri dishes. Adherent monocytes were incubated for 24-hours in serum-free conditions and in the presence of human recombinant leptin (0.1-5nM). Then TGF-b1 mRNA expression from these cells was evaluated by Northern blot analysis.
TGF-b1 was significantly elevated in 46 hypertensive obese patients as compared with TGF-b1 levels of 29 hypertensive patients with normal BMI (8.6±3 ng/ml vs 4.4±2 ng/ml, $P<0.001$). TGF-b1 circulating levels were strongly associated with BMI and leptin levels in an univariate analysis ($r=0.59$, $P<0.0001$; $r=0.62$, $P<0.0001$, respectively) and these associations were still present after stepwise multivariate analysis.The results of a 12-week calories-restricted diet produced a weight loss of 10% and a parallel decrease in TGF-b1 (from 8.9±3 ng/ml to 5.3±2.8 ng/ml; $P<0.01$) and leptin levels (from 30±24 ng/ml to 17±14 ng/ml, $P<0.05$). In vitro experiments showed that leptin is able to induce a dose-dependent increase in TGF-b1 production (from 1.6±0.3 ng/ml to 3.6±0.7 ng/ml) and mRNA expression (about 2.5 fold increase)in human peripheral monocyte cultures.
Our data indicate that TGF-b1 levels are positively associated with BMI and leptin levels in hypertensive patients and suggest that adipose tissue may be an important determinant of TGF-b1 levels possibly by a leptin-dependent pathway.

3263 The effect of 17β-oestradiol on markers of vascular inflammation in postmenopausal women: a randomized, controlled trial

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Background: Intervention trials in postmenopausal women with coronary artery disease have failed to demonstrate beneficial effects of hormone replacement therapy (HRT) on the course of disease, potentially due to proinflammatory effects of conjugated equine estrogens (CEE). Novel hormone formulations might exhibit a more favourable balance between cardiovascular risk and benefit.
Subjects and Methods: We characterized the effects of 48 weeks of treatment with 2 17beta-estradiol based HRT regimens on nonspecific (high sensitivity C-reactive protein [CRP], blood sedimentation rate [BSR], fibrinogen) and specific (cell adhesion molecules: ICAM-1, VCAM-1, E-selectin) markers of inflammation. Healthy postmenopausal women with subclinical atherosclerosis (i.e., increased carotid artery intima-media thickness of >1mm) randomly received either no HRT (n=73), or 1 mg 17beta-estradiol daily plus 25 mg gestodene for the last 12 days of each 28 day cycle (=standard dose progestin; n=65), or gestodene added each third cycle only (=low dose progestin; n=65). CRP was assessed by high-sensitivity assay.
Results: Groups were comparable regarding all baseline characteristics. No effect of either HRT regimen was observed on CRP levels, leukocyte count and neutrophils. Both HRT regimens reduced levels of ICAM-1 (-9%), VCAM-1 (-9%), E-selectin (-11%), fibrinogen (-12%), BSR (-5%), FSH (-44%) (all $p<0.001$). A modest effect on total (-6%; p=0.003) and LDL cholesterol (-7%; p=0.001)was seen. Subgroups of smokers and subjects on antihypertensive or lipid lowering medication showed effects comparable to the whole cohort. Effects of low and standard dose progestin were not different.
Conclusion: Our data indicate that HRT based on 17beta-estradiol favourably influences markers of vascular inflammation without a concomitant rise in hs-CRP. This finding adds new data to the ongoing discussion of the risks and benefits of HRT.

3264 Role of AT1 receptors and calcium influx in enhancing oxidative stress in hypertension

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Background: Recent studies provided experimental evidence that hypertension induces atherogenesis through enhanced oxidative stress and that angiotensin converting enzyme (ACE) system activation may play a pivotal role. AT1 receptors have been shown in vitro to enhance formation of superoxide anion (O2-). It has never been studied if this occurs also in human hypertension.
Methods: Forty-four hypertensive patients were randomly allocated to a treatment with ibesartan, an inhibitor of AT1 receptors, and life-style modification only. In each patients platelet platelet O2- production by chemiluminescience of lucigenin was studied before and after 4 weeks of treatment. Fourty healthy subjects matched for sex and age were also studied as control. To further analyse O2- production we performed an in vitro study using dihydroetidium as probe in a cytofluorimetric assay. The role of calcium in inducing angiotensin II mediated O2- production was analysed. Platelet suspension was added with dihydrothidium (160 μmol/L) and 50 μH calcium, incubated with or without irbesartan (1-3-10 nM 30 min 37C°), and stimulated with angiotensin II (2 μM).Calcium influx measurement was performed using the fluorescent indicator dye Fura-2 and the calcium surrogare Mn2+.
Results: Compared to healthy subjects, hypertensive patients had higher platelet production of O2- (2,68±0,57 vs 0,85±0,22) ($p<0.001$); there was not correlation between blood pressure and platelet O2- production. After treatment no changes of platelet O2- formation was observed in patients allocated to life-style modification; conversely in patients treated with ibesartan was demonstrated a significant decrease of platelet O2- production (2,69±0,63 vs 1,73±0,41) ($p<0,002$), that, however, was not correlated with blood pressure lowering. Platelet O2- production upon stimulation with angiotensin II (2 μM) in presence of calcium (50 μM) was 7.0+0.6. Irbesartan (1-3-10 nM) inhibited in a dose dependent manner the angiotensin II mediated O2- production (22%, 53% and 72% respectively, $p<0.005$). Angiotensin II (2 μM) induced calcium influx (80%). Irbesartan (1-3-10 nM) inhibited of 48%, 70% and 85% respectively the angiotensin II induced O2- production ($p<0.001$).
Conclusion: Patients with hypertension has enhanced formation of O2-, that is mediated by AT1 receptor upregulation.In vitro study demonstrated that AGII facilitates the influx of calcium into platelets and underscored the role of AT1 in eliciting such effect.This finding provides new insight to understanding the proatherogenetic activity of ACE system in humans.

LEFT VENTRICULAR REMODELLING AFTER MYOCARDIAL INFARCTION

3265 Prolonged activation of P38 MAPK following acute myocardial infarction; significance for myocardial remodelling

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Background: P38 MAPK is an important mediator for the signal transduction of major neurohumoral, inflammatory and mechanical stimuli relevant for the remodelling process following acute myocardial infarction (AMI). In vitro experiments have shown an activation of p38 mitogen activated protein kinase (MAPK) in states of acute ischemia and a role of this kinase in cardiomyocyte hypertrophy. So far, extent and time course of p38 MAPK activation have not been investigated in an in vivo model of myocardial infarction.
Methods: Left coronary artery ligation was performed in adult male Lewis rats. Sham operated animals served as controls. The AMI size was assessed in vivo by echocardiography and by visual inspection at organ harvesting. P38 MAPK activity in the left ventricular myocardium was detected by a non-radioactive MAP Kinase Assay and by Western Blot at 15 minutes, 1, 4 and 24 hours, 1, 3 and 6 weeks following AMI. Left ventricular expression of atrial natriuretic peptide (ANP) was measured by an ELISA technique, as ANP-expression is considered an established parameter of myocardial remodeling. At each time interval post AMI a minimum of 10 animals was sacrificed (4 sham-operated, 6 AMI).
Results: Compared with the sham operated hearts, P38 MAPK activation was found increased in AMI hearts at all time intervals. Two peaks of p38 MAPK activation were detected at 4 hours and at 1 week following AMI. At all time intervals post AMI higher p38 MAPK activity values were found in medium sized and large AMIs than in small ones. Expression of ANP was not detected in sham-operated, but in AMI hearts and was more pronounced in medium sized and large AMIs. However, the extent of p38 MAPK activation and the LV-expression of ANP did not closely correlate.
Conclusion: Investigating the first 6 weeks post AMI this study to our knowledge shows for the first time a long-term activation of p38 MAPK in vivo. The relationship between p38 MAPK activation and ANP expression with infarct size suggests a potential role of p38 MAPK in the remodeling following AMI.

3266 Up-regulation of CTGF following myocardial infarction in the rat and correlation with a1 (I) procollagen and TGFβ1 gene expression

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Background: One of the major mechanisms associated with adverse cardiac remodeling post-myocardial infarction (MI) is the pathological deposition of extracellular matrix material (fibrosis). Neurohormonal (NH) peptides e.g. angiotensin II (AngII) and endothelin (ET-1) have been implicated in this process, at least in part via down-stream activation of the profibrogenic peptide, transforming growth factor beta 1 (TGFb1). Connective tissue growth factor (CTGF) may be the final common mediator of fibrosis and in vitro data suggests that TGFb1 is a potent stimulus of CTGF. However, it remains uncertain whether similar interactions play a role in fibrotic processes in vivo. Therefore, the purpose of this study was to determine whether CTGF expression post-MI (i) is associated with parallel changes to collagen expression and (ii) whether this may be mediated via upstream TGFb1 expression.
Methods: Female Sprague Dawley rats underwent permanent ligation of the LAD to induce MI. Following confirmation of moderate-sized infarcts by ECG 24 hours post-MI, animals were randomised to 1-week treatment with either an AngII receptor antagonist (valsartan; ATRA, n=8), an ET-1 receptor antagonist (bosentan; ETRA, n=7) or combined treatment (AT/ETRA, n=8). Control animals received vehicle (n=8). Sham animals (n=8) underwent operation without ligation. Whole heart was harvested for total RNA extraction and Northern blot analysis of CTGF, TGFb1 and a1(I) procollagen mRNA transcripts.
Results: CTGF gene expression was increased by 137±28% in untreated MI animals compared to sham controls. Similarly, MI resulted in a 167±22% increase in TGFb1 ($P<0.01$) and a 862±22% increase in alpha (a)1(I) procollagen mRNA transcripts ($P<0.001$) compared to sham. NH blockade with ATRA, ETRA or AT/ETRA attenuated the increase in CTGF gene expression by 21±4%, 18±1% and 14±2% compared to vehicle post-MI. Importantly, there was a strong positive correlation observed between CTGF and a1(I) procollagen gene expression ($r=0.84$; $P<0.001$) amongst MI animals across all treatment groups. Furthermore, CTGF message correlated with TGFb1 mRNA transcripts ($r=0.76$; $P<0.001$). Conclusions: These data demonstrate a strong association between CTGF and (i) a1(I) procollagen message, supporting an important role for CTGF in mediating pathological fibrosis post-MI, and (ii) TGFb1 gene expression, suggesting that CTGF is regulated, at least in part, by endogenous activation of TGFb1 within the injured myocardium.

3267 Plasma BNP versus clinical, echo and angiographic variables for predicting early left ventricular remodelling and death after reperfused acute myocardial infarction and left ventricular dysfunction

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Background: Plasma brain natriuretic peptide (BNP) is an independent predictor of long-term LV remodeling and survival in thrombolized AMI patients (pts). However, information on prognostic role of BNP as compared to well established clinical, echo and angiographic prognostic predictors in pts with reperfused AMI and LV dysfunction are still missing. OBJECTIVE: To assess whether BNP measured at 1 and 3 days can independently predict 30-day LV remodeling and cardiac death after a first AMI and LV dysfunction successfully treated with primary PTCA. METHODS: In 31 pts with first AMI and LV dysfunction (ejection fraction =EF <40%), venous blood samples for analysis of BNP were obtained on day 1 (about 16 hours after admission), and on day 3 after AMI. All pts underwent 2-D echo examination within 24 hours of admission and at 3 day to assess both systolic and diastolic LV function. Repeat 2-D echo examination, and coronary angiography were obtained at 30 days after the index infarction. An increase in end-diastolic volume index (EDVI) > 20% from baseline to 1-month was defined LV remodeling. RESULTS: Pts were divided in 2 groups according to the 75th percentile concentration of BNP (251 pg/ml), (Group 1: high BNP, n=11; Group 2: low BNP; n=20). Pts of Group 1 had significantly greater baseline end-diastolic and end-systolic volumes (72 ± 17 ml vs 56 ± 12 ml, p = 0.005 and 50 ± 9 ml vs 32 ± 9 ml, p < 0.0001, respectively), and lower LVEF (30 ± 7% vs 42 ± 6%; p < 0.0001) and Doppler-derived mitral deceleration time (DT: 147 ± 42 msec. vs 183 ± 42 msec; p = 0.03) than pts of Group 2. No other significant differences between the two groups were found regarding demographic, clinical and echo variables. Patency and restenosis rate at 1 month were similar in the two groups. At 1 month, 4 pts (13%) died, and LV remodeling occurred in 9 (33%) of 29 survived pts. All four deaths occurred in Group 1; the prevalence of LV remodeling (75% vs 25%; p = 0.03) was significantly greater in Group 1 than in Group 2. However, only BNP measured at day 3 was significantly related to 1-month LV remodeling and survival. Moreover, by logistic regression analysis of clinical, non-invasive and angiographic variables, only DT, but not BNP, was an independent predictor of LV remodeling and survival (p = 0.04). CONCLUSION: In pts with reperfused AMI and LV dysfunction plasma BNP at day 3, but not at day 1, is related to 30-day LV remodeling and survival. However, BNP does not provide any incremental prognostic information when compared to other simple echo prognostic indicators, such as Doppler DT.

3268 Correlation of plasma MMP-2 and MMP-9 with N-BNP and with left ventricular function and volumes after acute myocardial infarction

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Following acute MI (AMI), plasma levels of N terminal pro BNP (NT) relate inversely to LV function and prognosis. Matrix metalloproteinases (MMP) may play a role in LV remodelling after MI and heart failure (HF). We investigated profiles of plasma MMP2 and MMP9 after MI and relationship with plasma NBNP and echo-cardiographic measures of LV dysfunction. Plasma NT and MMP levels were measured on each day 1-5 in 60 patients (45 male,mean age 64, range 36-87) after acute MI (39 anterior, 21 inferior). Echo studies for assessment of LV end systolic (ESV), end diastolic (EDV) volume and wall motion index (WMI) were performed during admission (ESV1,EDV1,WMI1) and at 6 weeks (ESV2,EDV2,WMI2; n=52). WMI1 (median=1.2) and WMI2 (1.5) correlated (p<0.0005). NT was elevated (Anterior median 1384 fmol/ml; Inferior 554 fmol/ml) and correlated with WMI1 (day 3 NT; r= -0.57,p<0.0005) and WMI2 (day 3 r=-0.37,p=0.04). MMP2 increased from day 1 (median 417,range 257-1800 ng/ml)- day 5 (501,310-2130) and on days 1-3 was higher in inferior compared to anterior MI (p<0.05). Plasma MMP9 showed a biphasic response, most prominent in anterior MI, with nadir on day 2 (median 4.55, range 0-111 ng/ml)and peak on day 4 (8.5, 0-641)(p=0.06).

Plasma NT correlated strongly with MMP9 after anterior (day4 MMP9 r=0.6, p=0.001; peak MMP9 r=0.57, p<0.001) but not inferior MI. There was borderline correlation of NT with MMP2 on days 3 (r=0.3, p=0.08) and 4 (r=0.37, p=0.054) after anterior MI.

For anterior MI, MMP9 correlated with EDV1 (r=0.72, p=0.004), ESV1(r=0.71, p= 0.005),and ESV2 (r=0.47,p=0.05).MMP2 correlated negatively with EDV1 (r = -0.64), ESV1 (r = -0.57), EDV2 (r = -0.56), ESV2 (r = -0.55)(All p<0.05). MMP9 but not MMP2 correlated with WMI1 (r=-0.70, p<0.0005). For inferior MI, there was borderline correlation of MMP2 and WMI1 and WMI2 (r=-0.4, p=0.07). Peak CK did not correlate with NT, MMP2 or MMP9.

Conclusion: After AMI,particularly anterior,there is a strong correlation between plasma MMP9 and NT. MMP9 correlates positively with LV volumes during, and 6 weeks after, admission. In contrast MMP2 correlates strongly but negatively with these parameters. Plasma MMP9 also correlates with LV function as assessed by WMI.This is the first evidence of differential relationship of plasma levels of individual MMPs with LV function and remodelling after AMI. Differential responses of MMPs may play a role in remodelling after AMI. Selective inhibition of MMPs may represent a therapeutic target in patients at risk of ventricular remodelling after AMI.

3269 Activated TGF-β1-TAK1-p38MAPK pathway in spared myocardium and its relation to ventricular remodelling after myocardial infarction in rats

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Background: It has been reported that TGF-beta1 alters myocardial gene expression resulting in myocyte hypertrophy. Two signaling pathways, Smad and TGF-beata1-activated kinase (TAK) 1, have been known in the signal transduction of TGF-beta1. However, its signal pathway in cardiomyocytes remains unknown.

Methods: We examined the changes of the TGF-beta1 signaling pathway in non-infarcted tissue by Western blotting and their relation to ventricular remodeling (n=6 for each group) after myocardial infarction (MI) in rats.

Results: The protein level of TGF-beta1 increased by 1.38±0.01-, 2.59±0.10-, 2.34±0.06-, 1.57±0.03-fold (p<0.01) compared with sham-operated rats(SR) 1, 3, 7 and 14 days after MI, and the TGF-beta1 receptor (TbetaR) II protein level increased 1.50±0.05-, 1.83±0.02-, 1.60±0.06- and 1.51±0.03-fold (p<0.01 compared with SR), respectively. The expression level of TbetaRI was significantly increased 3 and 7 days after MI (1.60±0.08- and 1.35±0.03-fold, p<0.01), respectively. The protein level of TAK1 was significantly (p<0.01) increased by 1.66±0.14-, 1.97±0.16- and 1.57±0.07-fold compared to that from SR at 1, 3, and 7 days post-infarct. There was no difference in the protein levels of MKK6 and p38MAPK among each group. However, phosphorylated MKK6 was increased by 2.20±0.19-, 2.55±0.47- and 3.29±0.32-fold (p<0.01), and phosphorylated p38MAPK was also increased by 1.90±0.03-, 2.03±0.06- and 2.35±0.06-fold (p<0.01) compared with SR 1, 3 and 7 days after MI. Immunoreactive staining of TGF-beta1, TbetaRI and TbetaRII was observed in cardiomyocytes, vascular smooth muscle cells and fibroblasts. In contrast, immunoreactivity of TAK1 was mainly localized to cardiomyocytes. mRNA levels of ANP and beta-MHC determined by competitive RT-PCR were significantly increased in ventricles after MI compared with SR (p<0.01 at each time point). Left ventricular diastolic and systolic dimensions determined by echocardiography were rapidly increased in the acute phase of MI, and additional changes were observed by 2 weeks (p<0.01 at each time point compared with SR). Posterior wall thickness was increased; however, relative wall thickness was decreased in the rats with MI.

Conclusion: The activated TGF-beta1-TAK1-MKK6-p38MAPK pathway paralleled the increased expression of ANP and beta-MHC during acute MI. Thus, this pathway in cardiomyocytes may play an important role in the ventricular hypertrophy of non-infarcted regions and in the ventricular remodeling after MI in rats.

3270 Impact of microvascular obstruction on left ventricular remodelling and long-term clinical outcome after reperfused acute myocardial infarction

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Background: The relation between microvascular obstruction (MO), left ventricular (LV) remodeling and long-term clinical outcome after AMI has still to be elucidated. We hypothesized that a preserved microvascular integrity in the area at risk (AAR) would favourably influence LV remodeling and prognosis.
Methods: One-hundred unselected patients (pts) with AMI successfully treated with primary PTCA underwent intracoronary myocardial contrast echocardiography (MCE) before and shortly after PTCA. Baseline (3±1 days), 1 and 6-month complete 2D-echo were obtained in 85 pts. Infarct zone wall motion score index (IZWMSI, from 1=normal to 4=dyskinetic), end-diastolic (EDV) and end-systolic (ESV) LV volumes, and ejection fraction (EF) were calculated. Repeat coronary angiography was obtained 6 months after AMI in 94 pts. Myocardial perfusion in the AAR was graded semiquantitatively as 0 (no visible contrast effect), 1 (patchy myocardial contrast enhancement), and 2 (homogeneous contrast effect). In each pts a MCE score index (MCESI) of AAR was derived by averaging the single segment score within the AAR. A pts was considered to have adequate reperfusion if MCESI was ≥1. Long term (3.4±1.9 years) clinical follow-up were collected for all pts.
Results: After PTCA 82 pts showed adequate myocardial reperfusion in the AAR (R), while 18 did not (NR). Baseline clinical and angiographic characteristics were similar between the 2 groups. However, NR pts had a higher peak creatine kinase (4126±2781 vs 2759±1771 U/L; p=.001), baseline IZWMSI (2.61±0.31 vs 2.24±0.43; p=.001), and a lower baseline EF (32±9 vs 40±7%; p=.001). At 6 month patency and restenosis rate were similar between the 2 groups. From day 3 on LV volumes progressively increased in the NR pts (n=13) and were larger than those of R pts (n=72) at 6 months (LV EDV: 171±61 vs 115±30 mL; LV ESV: 115±61 vs 59±26 mL; ANOVA p<.0001 for both). By stepwise multiple regression analysis MO was the most important independent predictor of late LV dilation (p=.0001) even adjusted for enzymatic infarct size. By Cox multivariate analysis MO represents the only strong predictor of cardiac death (p=.004) and combined events (cardiac death, nonfatal reinfarction, and hospitalization for heart failure; p=.01). Pts with microvascular integrity showed significantly better survival in terms of cardiac death (p=.0001, by log-rank) and combined events (p=.003, by log-rank).
Conclusions: In successfully reperfused AMI, MO within the risk area is an important predictor of both postinfarction LV remodeling and unfavorable long-term clinical outcome.

TRENDS IN CARDIOVASCULAR DISEASE IN EUROPE

3271 Are social gradients in cardiovascular risk factors widening or narrowing: ten-year trends in the Glasgow MONICA project?

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Introduction The MONICA inner-city population of Glasgow has high coronary event rates and high levels of social deprivation. Sociologists warn of polarization and alienation of deprived groups and the threat this poses to narrowing the social gradients in disease. We examined our survey data to see whether the risk factors that we measured showed evidence that social gradients widened or narrowed in the decade 1986-95.
Methods We examined data from surveys in 1986, 1989, 1992 and 1995, calculating age- standadized mean risk factor levels for men and women aged 25-64. A deprivation score was based on the postcode sector of residence of each person. We examined overall means and those in the least and most deprived quarters of each sex.
Results There were 2 859 men and 3 085 women aged 25-64. Response rates ranged from 60-65%. There were more social gradients in women than men overall. The following comments refer mainly to change in these gradients.
Cigarette smoking: no change in existing social gradients over time in either sex.
Systolic blood pressure: no gradient, no trend in men, gradient no trend in women.
Diastolic blood pressure: no change in women, paradoxical significant change in men from positive gradient (higher in more deprived group) to the reverse.
Total cholesterol: no gradient in men, no trend, no time trend in gradient in women.
HDL-cholesterol: no gradient in men, no change, gradient in women, no change.
Body mass index: no change in gradient in women, paradoxical significant trend in men from positive to negative gradient.
Consumption of fruit and green vegetables no change in gradient in either sex, but increasing gradient for skimmed milk in women.
The Dundee Coronary Risk Score: no change in existing strong gradient in either sex.
Conclusions Over ten years there was no consistent trend of widening social gradients in either sex. In men two related risk factors (diastolic blood pressure and obesity) showed significant reversal from positive to negative social gradient. For these factors there was no difference if all the survey results were averaged, but over ten years the the least and most deprived had changed places. Women, who showed many static social gradients, had a widening gradient for one dietary factor over the ten years of study. We therefore found no overall evidence of widening or narrowing of existing social gradients for risk factors, although there was an overall tendency to slow improvement.

3272 Age at hospital admission suggests delay in coronary heart disease presentation not prevention: trends over 20 years in 23,422 individual patients

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Background: There is increasing evidence that the decrease in age-adjusted coronary heart disease mortality is an artifact of age adjustment and does not represent a true reduction in the incidence of disease, rather a delay in the age of presentation.
Methods: This study examined the age at presentation in all patients with coronary heart disease: discharge diagnosis (ICD-9CM 410-414), during the years 1980 to 2000 who had been admitted to Auckland and Green Lane Hospitals (1200 bed tertiary referral centre). The unique patient identifier code was matched to a national mortality database and the vital status of each patient ascertained. The age/sex structure of the referring population was taken from national census figures. Years between the four yearly census cycle were estimated from linear interpolation.
Results: Between 1980 and 2000 there were 47, 875 discharges in 23,422 individuals. Using the first admission per patient (n=23,422), the average age at presentation in 1980 was 56 years (SD 12) rising to 72 years (SD 13) in 2000 at 0.65 years of age per year (P<0.0001 for linear trend). From 1980 to 1985 19% of all coronary heart disease admissions were in people aged 65 or greater compared with 28% in 1995 to 2000 (P< 0.0001). The proportion of women admitted increased in a linear manner from 31% in 1980 to 48% in 2000 (P<0.0001). Direct standardisation to the Auckland population produced age/sex adjusted admission rates of 0.4 per 1000 population in 1980 and 8.1 per 1000 population in 2000.
During the same time period, length of stay decreased at a rate of 0.25 days per year (P <0.0001 for linear trend) from a median 8 days (IQR 6-10) in 1980 to a median 4 days (IQR 2-8) in 2000.
Conclusion: The age at first presentation with coronary heart disease has increased by 13 years over 2 decades. In addition, more first coronary heart disease admissions are seen in the elderly than would be predicted by the aging New Zealand population, alone. These data suggest that coronary heart disease is delayed, not prevented.

3273 Atrial fibrillation and the ageing population: an emerging epidemic?

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Aims: Atrial fibrillation (AF) is the most common cardiac arrhythmia and an important cause of cardiovascular morbidity and mortality (particularly in relation to stroke and heart failure). This study examined the likely burden of AF in respect to its population prevalence among those aged 45 years or more, in addition to the number of hospital admissions associated with a principal diagnosis of AF in the UK for the period 2000-2020.
Methods: We applied contemporary UK-specific estimates of the population prevalence of AF and the rate of hospital admissions associated with a prinicpal diagnosis of AF (on an age and sex-specific basis), to projected changes in the UK population for the years 2000, 2005, 2010 and 2020. Using recent trends analyses, in addition to population changes alone, we also considered the likely (additional) impact of underlying increases in the prevalence of AF and related hospitalisations.
Results: We estimate that in the year 2000 there were approximately 290,000 men and 254,000 women aged 45 years or more being actively treated for AF in the UK: a combined total of 544,000 individuals representing just under 1% of the UK population overall. Based on population changes alone (i.e. stable prevalence rates) we estimate the number of men and women being treated for AF will have increased by 33% and 18%, respectively, by 2020. If combined with a modest 5% rate increase in the prevalence of AF every 5 years across all age groups (due to a greater burden of contributory cardiovascular disease states), these figures will increase by 54% and 33%, respectively, with about 1.3% of the UK population affected by 2020. In both models, the greatest increases are predicted to occur in the period 2010-2020 because of the ageing "Baby Boomer" population cohort. We also estimate that there were 37,500 male and 38,300 female admissions for AF (principal diagnosis) in the UK during the year 2000. Based on population changes alone, these admissions are predicted to rise by 31% and 16%, respectively, by 2020. If, however, current trends in the rate of increase of such admissions are maintained, these figures are predicted to rise by 395% and 325%, respectively. Once again, the greatest increases are likely to occur between 2010 and 2020.
Conclusions: In this unique study, we have shown that AF already represents a major health problem within the UK population. Furthermore, without substantial changes in relation to its prevention and treatment, the burden of AF (particularly as a precursor of stroke and heart failure)is likely to rise substantially in the next 20 years.

3274 Cardiovascular risk factors and therapeutic management of patients with stable coronary artery disease: a nationwide French survey

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Aims: To assess prevalence and control of cardiovascular risk factors as well as therapeutic management of French patients (pts) with stable coronary artery disease (CAD)in 2001.
Methods: The 6 first consecutive pts with CAD presenting to a cardiologist were included if they met the following criteria: prior acute myocardial infarction (AMI), prior PTCA or CABG or documented stable angina.The following data were collected: demographics, cardiovascular history, risk factors, blood pressure (BP), last record of LDL-cholesterol and cardiovascular therapeutics.
Results: 6349 pts (81% men) aged 67±10 years were included by 795 french cardiologists. Previous risk factors were: hypertension (50%), hypercholesterolemia (75%), current smoking within 3-months period(9%) and diabetes (16%). Previous AMI was observed in 51% of pts and previous angina in 59% of pts.The 140/90 mmHg BP goal was obtained in 56% of pts (41% in pts with treated hypertension vs 70% in pts not receiving antihypertensive drugs for hypertension). BP control in pts with diabetes was only 44%. The LDL-c goal less than 3.4mmol/l was obtained in 58% of pts (60% in pts treated by lipid lowering agents vs 53% in not treated pts).Aspirin or other antiplatelet agents were used by 84%, statins by 65%, beta-blockers by 64% and Ace-Inhibitors by 33% of pts respectively. In pts with prior AMI the use of beta-blockers rose to 68% and the use of ACE-inhibitors to 41%. In pts with diabetes the use of beta-blockers fell to 60% and the use of ACE-inhibitors rose to 47%.
Conclusion: ESPOIR was a nationwide study representative of french pts with stable CAD. Prevalence of modifiable risk factors remains high and blood pressure as well as cholesterol goal were not satisfactorily achieved. A slow incorporation of secondary prevention strategies was observed mainly regarding the use of ACE-inhibitors.

3275 The associations between climatological variations and cardiovascular mortality, in greater Athens area, during 15 years period (1987–2001)

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Background: The fact that environmental conditions are associated with the pathogenesis of physical disease was known as early as the time of Hippocrates. The aim of this study is to evaluate the association between climatological variations, with cardiovascular mortality, on the greater Athens area inhabitants.
Methods: We studied mean monthly values of air temperature and relative humidity (data from the National Observatory of Athens) as well as the cardiovascular mortality (local registers), during 1987-2001. In order to evaluate the association between cardiovascular mortality and the climatological variations we applied a special, empirically determined temperature-humidity index (T.H.I.), suggested by E. C. Thom (T.H.I. = Ta - 0.55*(1 - 0.01 RH)*(Ta - 14.5), Ta = mean monthly dry-bulb air temperature in oC, RH = mean monthly relative humidity in %). Statistical analysis was based on Poisson regression models, after taking into account the effect of age group, seasonality, air pollution, and the number of holidays and strikes (confounders).
Results: An age-adjusted positive trend in CHD mortality was observed during the investigated period (+26% in all ages, $p < 0.001$ and +32% in >75 years old group, $p < 0.001$). Additionally, CHD mortality was positively related with relative humidity ($p<0.001$) and inversely associated ($p < 0.01$) with mean air temperature, during the studied period. Moreover, a consistent association between T.H.I. and CHD deaths was found (b=-0.72, $p < 0.001$), with more significant results in the elderly ($p < 0.0001$). In particular, a 10-unit decrease in the T.H.I. scale raises by 20% the monthly cardiovascular mortality ($p < 0.001$), while T.H.I. < 24 increase by 53% the risk (odds ratio = 1.53, $p < 0.05$) of observing the daily number of cardiovascular deaths in the upper quartile (i.e. > 42 deaths/day) compared to the lower quartile (i.e. < 29 deaths/day).
Conclusions: Our findings suggest that a strong association between climatological variations and CHD mortality seems to exist. The suggested cut-off point of 24 in the T.H.I. scale could be a useful tool in public health practice, in order to reduce mortality rates, especially in countries with extreme environmental phenomena. The previous findings are in accordance to the reports from other studies, especially, in the US, but it is hard to claim that they support evidence for causality. Thus, further research is needed in order to investigate the mechanisms by which environmental conditions affect CHD mortality.

3276 Plasma lipids and sex hormones among 366 men from France and Northern Ireland

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Background The prevalence of coronary heart disease (CHD) is much higher in men than in women, even after adjustment on known independent cardiovascular risk factors. An explanation of these sex differences could be that sex hormones may play a role in the pathogenesis of CHD, probably through their associations with plasma lipids. The aim of this cross-sectional study was to assess the relationship between sex hormones and plasma lipids in a population-based sample.

Methods Subjects were 366 men, 50 - 59 years old, selected in France (Lille, Strasbourg and Toulouse) and Northern-Ireland (Belfast) and examined between 1991 and 1993. Socio-economic, tobacco consumption and physical activity data were obtained by questionnaire. Medical examination included blood pressure (BP) and anthropometric measurements. A blood sample was obtained for the measurement of biological parameters (triglycerides (TG), high-density-lipoprotein cholesterol (HDL-C), total testosterone (TT), estradiol (E2) and sex-hormone-binding-globulin (SHBG)). Low-density-lipoprotein cholesterol (LDL-C) was calculated using Planella's formula. Pearson correlation coefficients and student's t tests were used to identify factors associated with plasma lipids. Multiple linear regression models were used for multivariate analyses, using TG (log-transformed) and HDL-C as dependent variables. The effect of sex hormones on plasma lipids was estimated after adjustment for age, body mass index (BMI), systolic BP, smoking, alcohol intake and physical activity.

Results SHBG and TT were negatively correlated with TG ($p<0.0001$ and $p<0.04$, respectively) and positively correlated with HDL-C ($p<0.0001$ and $p<0.01$). E2 was positively correlated with TG ($p<0.03$). No significant association was found between sex-hormones and LDL-C. In multiple linear regression analyses, after multiple adjustment, SHBG and E2 remained significantly ($p<0.01$ and $p<0.05$, respectively) and independently associated with TG. SHBG remained also strongly associated with HDL-C ($p<0.0001$). The model including SHBG, E2 and adjustment variables explained 14.1% of TG variability, and SHBG and E2 accounted respectively for 16.4% and 7.0% of the model variation. The model including SHBG and adjustment variables explained 26.1% of HDL-C variability, and SHBG accounted for 29.0% of the model variation.

Conclusions After adjustment for confounders, SHBG was positively associated with HDL-C and negatively associated with TG, suggesting that SHBG may play an important role in the relationship between sex hormones and plasma lipids.

THE ROLE OF ASSIST DEVICES IN HEART FAILURE

3277 Early and mid-term results of the Harefield left ventricular assist device combination therapy for reversal of end stage heart failure

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We have previously described a strategy for reversal of end stage heart failure through induction of reverse remodelling using LVADs combined with pharmacological therapy, followed by induction of physiologic hypertrophy using the B2 agonist Clenbuterol. We present here the early and mid term results. From December 1999 to December 2001, 19 patients with idiopathic dilated cardiomyopathy (DCM) in end stage heart failure with deteriorating clinical status and evidence of secondary organ dysfunction were treated using this therapy. There were 15 males and 4 females aged 15 to 56 years. Diagnosis had been made a mean of 44 months before. None had histological evidence of myocarditis. Eighteen received HeartMate 1 and 1 received HeartMate II. There were 3 (15.8%) deaths in the peri-operative period and 1 late death due to infection. Patients underwent sequential echocardiographic, exercise capacity and oxygen consumption assessment with the pump switched off under full heparinisation at fortnightly intervals following the first month, and invasive haemodynamic investigation at 3 months. Duration of LVAD support ranged from 63 - 503 days, mean 276. During this period 11 (73.3%) of the survivors exhibited significant improvement as defined by a series of strict criteria. Of these 11, one was transplanted because of persistent native valve regurgitation, 1 is awaiting explantation and 9 (60% of survivors) have been successfully explanted. During a period of post explantation follow up ranging from 144 to 496 days, one patient developed lung carcinoma and is being treated by chemotherapy and radiotherapy. The remaining patients are completely asymptomatic and all have returned to their previous occupation. The mVO2 was a mean of 26mls/kg/min and ejection fraction was a mean of 69% at latest follow up. Invasive investigation performed at 6 monthly intervals showed a mean PA pressure of 15mmHg, PCWP of 9mmHg and cardiac output of 4.9 l/min at latest investigation. It is concluded that the combination therapy for reverse remodelling followed by induction of physiological hypertrophy gives encouraging early and mid-term results which may warrant extension of this form of therapy to less critically ill patients in a randomised trial.

3278 Six hundred patients supported by ventricular assist devices in Berlin

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Background Since 1987 we have used seven different types of ventricular assist devices in more than 600 patients. The aim of this study is to present our experience.

Patients and Methods: Between April 1987 and January 2002, 620 ventricular assist devices were implanted in 604 patients [male, 498 (82%); female 106 (18%)]. The mean age was 48 years with a range of 3 days to 77 years [adults, n = 554 (92%), pediatric, n = 50 (8%)]. The indications for the use of a ventricular assist device were: a) profound cardiogenic shock [cardiomyopathy (ischemic = 37; dilative = 166; others 35 cases), or acute myocardial infarction (n = 41)], b) severe end-stage heart failure without cardiogenic shock [n = 160 (26%)] and c) inability to wean a patient from cardiopulmonary bypass (postcardiotomy heart failure) [n = 84 (14%)]. The intention was to support the patients as a bridge to heart transplantation, bridge to recovery or permanent support.

Results In 337 cases (55%) the ventricular assist device implanted was a biventricular, in 264 (43%) a left ventricular and in 19 (2%) a right ventricular support system. The pulsatile extracorporeal device Berlin Heart was implanted in 429 patients (69%) and an implantable left ventricular device of type Novacor in 113, HeartMate in 21, and LionHeart or Micromed DeBakey in 19 patients. The early mortality was significantly higher ($p<0.05$) in patients with preoperative profound cardiogenic shock (55%) and in the postcardiotomy group (74%) in comparison to patients with preoperative end-stage heart failure without shock (28%). One hundred and seventy-two patients (29%) were bridged to heart transplantation; there was no significant difference in long-term survival after heart transplantation in patients with and without previous ventricular assist device implantation. Removal of the device was performed in 43 (7%) patients after recovery of myocardial function. Thirty-three patients are currently on a device, 50% of them supported permanently.

Conclusion Implantation of a ventricular assist device may lead to recovery of the patients from secondary organ failure. When implanted in the situation without profound shock, the results are significantly better. Therefore, the patients with severe end-stage heart failure should be considered for possible implantation of a assist device before profound cardiogenic shock occurs.

3279 Long-term results with left ventricular assist devices as bridge to heart transplantation: the Niguarda experience

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Background: Congestive heart failure is the leading cause of death in western countries. Heart transplantation currently is the only accepted therapy for patients with end-stage heart failure but the supply of donor hearts is inadequate, and different mechanical circulatory support have been utilised as bridge to heart transplant.
Patients and Methods: Since April 1992, 53 patients (47 man, 6 women, 43,1±12,5 years) with end-stage heart failure were assisted with an LVAD as bridge to heart transplant. The causes of heart failure were: dilated idiopathic cardiomyopathy in 39 (73.6%) pts, ischemic cardiomyopathy in 11 (20.7%), acute myocarditis in 3 (5.7%). The devices utilised were: Novacor LVAS in 31 (58,5%) patients, DeBakey VAD in 11 (20,7%), Thoratec in 7 (13.2%), Medos LVAD in 3 (5,6%), Abiomemd BVS 5000 in 1 (1,9%).
Results: All patients survived the operation. Mean duration of LVAD support was 2.8±5.6 months (range 1 day-38 months). Three patients were assisted for more than 1 year and 1 patient for more than 3 years; the cumulative time of support was 156 months. Thirty-seven patients (71.1%) underwent heart transplantation. Twelve major bleeding episodes requiring rethoracotomy occurred in 9 pts (16.9%). Major neurologic events (defined as neurologic deficit permanent or persistent for more than 24 hours) occurred in 6 patients (11,3%). Abdominal pocket infection (defined as the presence of local signs of infection with purulent secretion and positive bacterial cultures necessitating irrigation and drainage) occurred in 2 patient (3.77%). Septic complication (defined as the presence of body temperature above 38.5 °C, white blood cell > 12.000 gm/dL, positive blood cultures) occurred in 3 pts (5.6%).
Ten patients (19,9%) assisted with the Novacor Wearable LVAS device were discharged at home while waiting for HTx. The mean follow-up of 34 discharged transplanted patients was 45.3±37 months. Actuarial survival of transplanted patients while on LVAD was 91.0±4.9% and 83.4±8.5% at 1 and 5 year respectively. No differences in post-transplant long term survival, rejection and allograft vasculopathy occurred between patients transplanted with or without LVAD assistance.
Conclusions: LVAD therapy proved to be effective in bridging patients with end stage heart failure to HTx. While on LVAD support patients assisted with implantable wearable devices could be discharged at home ameliorating their quality of life. The excellent survival rate after HTx is concomitant with a low incidence of rejection and cardiac allograft vasculopathy.

3280 Initial and prolonged haemodynamic effects of intraaortic balloon support in ventricular septal defect complicating acute myocardial infarction

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Background: Immediate surgical repair of ventricular septal defect (VSD) complicating acute myocardial infarction is associated with high mortality. Preoperative use of an intraaortic balloon pump (IABP) is routinely recommended to achieve hemodynamic stabilization, which permits preoperative diagnostic examinations or even delayed surgical repair. However, there is no clear evidence of the hemodynamic effects of short-term and prolonged IABP support.
Methods: An IABP was implanted preoperatively from 12/1997 to 02/2002 in 20 consecutive patients with infarct-related VSD (11 men, 9 women, mean age 70±11, range 46-89). Effective cardiac output (l/min), left-to-right-shunt (l/min) and the shunt flow ratio were calculated by the method of Fick pre and post intraaortic balloon counterpulsation and at daily follow-up with pump "on" and "off".
Results: Effective cardiac output improved from 3.6±1.3 l/min to 4.2±1.3 l/min ($p<0.001$). Left-to-right-shunt was reduced from 7.3±3.5 l/min to 5.6±.3.3 l/min ($p<0.001$) and shunt flow ratio decreased from 3.1±0.9 to 2.5±0.7 ($p<0.001$) with IABP support. In patients undergoing delayed surgical repair (n=8) hemodynamic improvements were sustained over time (pump "on" vs. "off" $p<0.05$). Mortality in patients with early (day 1-2) operation was 71% and with delayed surgery (day 8-25) 22%, respectively.
Conclusions: In patients with infarct related VSD IABP support provides an immediate and sustained hemodynamic improvement resulting in an enhanced effective cardiac output and a reduced left-to-right-shunt and shunt flow ratio, which results in hemodynamic stabilization in at least some patients.

3281 Functional status of patients with chronic angina treated with Enhanced External Counterpulsation

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Introduction: Enhanced External Counterpulsation(EECP) is a non-invasive therapy, similar to the intra-aortic balloon pump, used for treatment of chronic angina in patients who are no longer considered suitable candidates for surgical or percutaneous revascularization. This study examined a group of patients both pre and immediately post a course of EECP treatment, to determine changes in functional status and factors affecting functional status.
Methods: The International EECP Patient Registry collects data on consecutive patients treated with EECP to determine safety and document both short and long term outcome. The functional status of a subgroup of 485 patients was assessed using the Duke Activity Status Index(DASI).
Results: Patients had a mean age of 67 ± 11 years, were mostly male(73%), and had long standing coronary disease (mean 12 ± 8 years, multivessel disease in over 70%). The majority had previous revascularization (71% PCI, 69% CABG) and 78% were no longer considered candidates for further revascularization. Severe (CCSC Class III/IV) angina was reported by 86% of patients, and 69% reported nitroglycerin use. Comorbidities were frequent: diabetes (43%), peripheral vascular disease (24%), congestive heart failure (25%). The mean DASI score pre-EECP was 12.8 ± 11.0, a very poor functional status similar to that previously reported for end stage coronary artery disease patients. Baseline factors associated with a low score were female gender ($p<0.01$),hypertension ($p<0.001$), hyperlipidemia($p<0.01$), congestive heart failure($p<0.01$), diabetes($p<0.05$),severe angina($p<0.001$) and unsuitability for further PCI or CABG ($p<0.001$). By multivariate regression analysis significant, independent factors predicting a low functional status pre-EECP were female gender, chf, diabetes, hypertension, severe angina and unsuitability for CABG. After a mean treatment course of 34 hours, 72% of patients reported a one or more class reduction in angina, and 47% of patients using nitroglycerin had discontinued its use. Mean DASI score post-EECP was 18.0 ± 13.4. Post-EECP DASI scores were significantly associated both with the score pre-EECP ($p<0.001$) and a reduction in angina class ($p<.001$).
Conclusions: Patients presenting for EECP treatment for chronic angina have a poor functional status. Functional status is dependent on severity of angina and presence of comorbidity and risk factors. Treatment with EECP not only reduces angina symptoms, but produces a concomitant increase in functional capacity similar to that seen 1 year after bypass surgery.

3282 Cardiogenic shock – Can mechanical circulatory support systems act as life-savers?

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Background: Despite many advances in drug therapy and medical technology cardiogenic shock (CS) is still associated with a high mortality rate (80-90%). To improve survival chances of patients suffering from cardiogenic shock, it is often necessary, despite critical conditions, to transport these patients to a highly specialized center where mechanical circulatory support systems (MCSS) are available. In 1991 our clinic established a special emergency transportation team to transfer the critically unstable patients from peripheral hospitals. Their mission was to stabilize their condition and transport them to our facility using the most effective methods.
Methods: In a retrospective study we examined the data of 43 patients to determine if the mortality rate was different when compared to conventionally treated patients.
Results: Between 1998 and July 2001, 43 patients (31 male, 12 female) with cardiogenic shock refractory to conventional therapy were referred to our team. All of them were on high doses of inotropic support agents and on respirators. They showed signs of multi-organ failure and some of them were already on IABP or ECMO. Etiology for the CS was as follows: acute myocardial infarction (34%), decompensated DCM (30%), myocarditis (18%) and the rest had miscellaneous causes including valvular disease, toxic heart failure, etc. (18%). Prior to transportation we initiated IABP in 20 patients and a centrifugal pump in 7 patients.
All together, 21 patients were released from the hospital. Of those, 19 are currently still alive. During hospitalization, 12 of these had a LVAD and 5 others a BiVAD. In total 8 patients received heart transplantations.
Conclusion: The survival rate of almost 50% in these critically ill patients, in our opinion, justifies the high expenses (time, energy, costs) of treating these patients who, for a large part, would otherwise die. It is felt that the use of MCSS plays a significant role in the reduction of mortality in this group of patients. Furthermore, this significant mortality difference would justify the establishment of other transportation teams with similar capabilities.

MANAGEMENT OF CONGENITAL HEART DISEASE IN GROWN-UPS

3283 The echocardiographic, neurohormonal and exercise capacity changes post transcatheter closure of atrial septal defects

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Introduction: Atrial septal defects(ASD) are the commonest congenital cardiac abnormality presenting in adult life. The transcatheter closure of these defects has become increasingly common over the past few years,however little is known about the follow-up of this group.Methods: 58 patients had successful closure of ASDs using the amplatzer device. A Full Bruce protocol exercise test with continual expired gas analysis was performed pre closure and at 82 ±63 days post closure. 18 patients performed the protocol at 10.02±6.14 months post closure. Predicted VO2 was calculated. Transthoracic echocardiography and transcranial Doppler with injection of agitated saline was performed at both time points. Venous blood was taken for measurement of Brain Natriuretic Peptide (BNP).Results: Paired t-tests were performed on the data.(Mean(SEM)).The mean age of the patients was 43.8± 14.9 years. Exercise time increased from 513s pre (36.9) to 564s(32.4) post (p=0.01) VO2 max. increased from 23.89 (1.18) pre to 25.36 (1.04) post (p=0.0001). Despite the improvement in VO2 max, it remained significantly less than predicted. (actual 25.36 (1.04), predicted 30.09 (1.39) p=0.001). This reduction in VO2 was still evident in the group at 10.02±6.14mths. (24.84(SEM1.77), predicted 31.52 (2.1) p=0.001). Right ventricular(RV) dimensions were reduced post closure (3.3cm(0.13), 2.82(0.08) p=0.0001) as was pulmonary artery pressure(PAP)(29.09mmHg (1.77), 20.32 (0.69) p=0.0001). Transcranial Doppler produced positive embolic signals in 25% of patients post closure compared to echocardiography in which 8% demonstrated a right to left shunt. Two contrasting patterns of BNP secretion were observed. In the group with a reduction in BNP (86.5(27.9) to 58.0(18.3) p=0.043), RV dimensions decreased (3.16(0.3),2.63 (0.1), p=0.031), PAP decreased (24(2.49),15.6 (0.4) p=0.014) and VO2 max increased (23.7(3.26), 25.6(2.93),p=0.046). This was in contrast to the group with an increase in BNP(9.2(3.2) to 40.0(13.6) p=0.05). In this group RV dimensions (2.98(0.36), 2.88(0.29), p=0.377), PAP (19.17(1.54), 19.17(1.54) and VO2 max (24.5(1.93), 24.9(2.29) p=0.063) showed no significant change. Conclusion: The transcatheter closure of ASDs results in significant improvement in echocardiographic measurements and exercise capacity post closure. BNP appears to reflect resultant change in these indices. Transcranial doppler is a sensitive technique for detecting right to left shunts.In combination with echocardiography it can assess the need for continuing antiplatelet therapy and further investigation.

3284 Increased carotid arterial wall thickness as an indicator of cardiovascular risk in adult patients succesfully operated for aortic coarctation

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Objectives: Despite succesful surgery of aortic coarctation cardiovascular mortality and morbidity, notably premature coronary artery disease and cerebrovascular accidents, are greatly increased in middle aged adult post-coarctectomy patients. This may be due to previous increased blood pressure in the pre-coarctatial arterial conduits. B-mode ultrasound imaging can describe status and changes in intima-media complex thickness (IMCT) of carotid and femoral arterial walls. IMTC is a non-invasive measure and considered a validated endpoint for atherosclerosis.

Methods:

Ultrasound investigations were done in 26 normotensive (31.7(SD9.1)years) and 22 hypertensive (34.2(9.6)years) adult post-coarctectomy patients, and in 26 age and sex matched controls (33.9(9.9)years). Mean age at operation was 9.5(range 0.8-22.1)years in normotensives and 8.5(0.1-26.9)years in hypertensives. A subject's IMTC was calculated as the averaged measurements of three right and three left carotid arterial wall segments. Hypertension was defined as the daytime mean systolic blood pressure above 140mmHg registered on 24 hour ambulatory blood pressure monitoring. Student's unpaired t-test was used to compare IMTC's of normotensive and hypertensive post-coarctectomy patients and controls.

Results: IMTC of the entire post-coarctectomy group (0.74(SD0.10)mm) was increased if compared to controls (IMTC=0.60(0.09)mm):DIMT=0.14mm, $p<0.0001$. Differences between normotensive (0.70(0.10)mm) and hypertensive (0.78(0.10)mm) patients and each of these groups with controls, were highly significant (all $p<0.0001$).

Conclusions: Normotensive as well as hypertensive post-coarctectomy patients showed increased carotid IMTC at relatively young age. The findings reflect increased vascular risk in all post-coarctectomy patients regardless of blood pressure and indicate the need for cardiovascular risk profile evaluation in all patients to improve vascular disease prevention.

3285 Late progression of pulmonary regurgitation in adults with repaired tetralogy of Fallot

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Background: Pulmonary regurgitation after repair of tetralogy of Fallot is associated with late morbidity and mortality. However, little is known about the rate of progression of pulmonary regurgitation.

Methods: Using cross sectional echocardiography we studied 60 consecutive adults with repaired tetralogy of Fallot (age 35±11 years, range 16-62 years, 23 females and 37 males). Severity of pulmonary regurgitation was assessed by the pulmonary regurgitant index (PRi: pulmonary regurgitant Doppler signal duration/total diastolic time). Patients with right ventricular outflow tract Doppler velocity >3m/s were excluded. Right ventricular end-diastolic diameter was measured using M-mode in the parasternal long axis view (RVDd) and at the inflow (RVDinflow) from the four-chamber view. Individual patients results were compared with corresponding indices derived from echocardiograms performed at least 30 months (mean 51±13, range 30-77 months) previously at this institution. Measurements were performed by a single blinded investigator.

Results: There was a significant decrease in PRi (0.85±1.4 vs 0.74±0.19, $p<0.0001$), denoting progression of pulmonary regurgitation. Forty (66%) patients had at least moderate pulmonary regurgitation at present compared to 26 (43%) at previous echocardiogram (Fisher's exact test, p=0.017). PRi correlated negatively with the color diameter of the pulmonary regurgitant jet both at current (r=-0.502, p=0.0002) and at initial echocardiogram (r=-0.643, $p<0.0001$). There was a tentative increase in RVDd (3.00±0.9cm vs 3.35±0.9cm, p=0.06) and RVDinflow (4.49±0.79cm vs 4.64±0.71cm, p=0.09) between the two echocardiograms.

Conclusions: Severity of pulmonary regurgitation progresses with time in adults with repaired tetralogy of Fallot. Early pulmonary valve implantation may therefore improve the very long-term outlook for these patients.

3286 Long-term outcomes up to 30 years after the Mustard or Senning operation: a nationwide multicentre study

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Patients with transposition of the great arteries (d-TGA), corrected with the Mustard or Senning operation, present with multiple problems during follow-up. This frequently complicates the long-term management of this patient population. This multicentre study assessed mortality, morbidity, functional abilities and social integration of patients up to 30 years after Mustard or Senning repair. Long-term outcomes of both procedures were compared.

Methods: We performed a retrospective review of medical records of all patients with simple or complex d-TGA, operated on and/or followed-up in Belgium. Three hundred thirty nine subjects were included, comprising 124 patients after Mustard and 215 patients after Senning repair. About two-third of the sample was male (64.6%). Simple d-TGA was observed in 244 patients (72%), while in the remaining 95 patients (28%) other cardiac lesions were associated, such as large VSD, pulmonary valve stenosis, or coarctation of the aorta.

Results: Overall mortality was 24.2%. Early mortality (<30 days after operation) accounted for 16.5%, while late mortality was observed in 7.7%. The actuarial survival of early survivors at 10, 20, 25 and 30 years after operation was 91.7%, 88.6%, 87.5%, and 79.3%, respectively. The Senning operation showed a slightly, but not significantly, better survival than the Mustard operation. Yet, baffle obstruction occurred more frequently after Mustard repair (15.3%) than after Senning repair (1.4%)($p<0.001$). A difference between the two types of operation was also observed for atrial flutter (20.5% vs. 1.8%), although this difference was due to the longer postoperative course of patients after Mustard operation (OR: 1.18; 95%CI: 1.05 – 1.33). Systemic ventricular dysfunction (moderate=9.5%; severe=2%) and tricuspid valve regurgitation (moderate=27.5%; severe=7.5%) did not significantly differ between the two procedures. Survivors of the Senning cohort showed a significantly better functional status ($p=0.023$), and more engagement in sport activities ($p<0.001$).

Conclusions: This nationwide multicentre study indicated that long-term outcomes after the Mustard and Senning operation were relatively favorable in terms of mortality, morbidity, functional status and social integration. Although overall mortality in the Senning cohort did not differ from the Mustard group, patients after Senning repair showed better functional status, higher participation in sport activities, and less baffle-related problems.

3287 Right ventricular ischaemic dysfunction during dobutamine stress in patients with Mustard repair for transposition of great arteries

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Background: Despite good functional capacity in patients with Mustard repair for transposition of great arteries (TGA) they are known to have impaired right ventricular (RV) function, the mechanism of which is unclear.

Aim: To assess RV electrical and mechanical response to stress and to explore possible mechanisms that may explain late development of RV dysfunction in these patients.

Methods: Twenty five patients (age 30±7 years, 13 male) were studied 25±6 years after Mustard repair using Doppler echocardiography, 12 lead ECG at rest and peak conventional dobutamine stress protocol and compared them with 15 controls of similar age. RV free wall and septal amplitude were measured from M-mode recording of the tricuspid ring movement and systolic and diastolic velocities using tissue Doppler technique. Patient's cardiopulmonary (MVO2) exercise tolerance was also assessed in the same day of the echocardiogram.

Results: Fourteen patient were in NYHA class I and 11 in class II. No patient developed stress related symptoms although all but one had RV amplitude less than the 95% CI of normal, $p<0.001$ at rest. Fifteen patients dropped or failed to increase RV free wall amplitude with stress in contrast to controls who increased their RV amplitude by 20%. Eighteen patients developed RV and/or septal incoordination (post-ejection shortening), $p<0.001$, eleven of whom demonstrated significant anteroseptal ST depression and/or T wave normalization, $p<0.001$. RV free wall amplitude and systolic velocities and septal amplitude correlated with MVO2 (r values 0.5, 0.72 and 0.64, respectively, $p<0.001$) Septal amplitude also correlated with peak aortic velocity ($r= 0.5$, $p<0.01$).

Conclusion: Although patients with Mustard repair for TGA tolerated pharmacological stress with no symptoms 72% demonstrated significant electrical and mechanical signs of ischaemic right ventricular dysfunction. These abnormalities are related to their limited cardiopulmonary exercise. Thus, stress related ischaemic changes may contribute to perpetual deterioration of right ventricular function known in this condition.

3288 Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease

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Background: Neurohormonal activation characterises chronic heart failure, relates to outcome and is a principal target for pharmacotherapy. It is not known whether a similar pattern of neurohormonal activation exists in adults with congenital heart disease and if so whether it relates to common measures of disease severity or whether cardiac anatomy is a better discriminant.

Methods: Concentrations of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), endothelin-1 (ET-1), renin, aldosterone, norepinephrine and epinephrine were determined in 53 adults with congenital heart disease, comprising 4 anatomical subgroups; fetralogy of Fallot, single ventricle physiology, right-sided systemic ventricle, miscellaneous (29 female; 33.5±1.5y, NYHA class 2.0 ± 0.1, mean ± SE) and 15 healthy control subjects (8 female; 32.3±1.3y). Systemic ventricular function was graded by a blinded, echocardiographer as being normal, or mild, moderately or severely impaired. Patients underwent cardiopulmonary exercise testing, and had chest x-ray, ECG and oximetry performed.

Results: Adults with congenital heart disease had elevated levels of ANP (56.6 vs 3.1 pmol/L), BNP (35.8 vs 5.7 pmol/L), ET-1 (2.5 vs 0.7 pmol/L, all $p<0.0001$), renin (147 vs 16.3 pmol/L), norepinephrine (2.2 vs 1.6 pmol/L, both $p<0.01$) and aldosterone (546 vs 337 pmol/L, $p<0.05$). There was a highly significant stepwise increase in ANP, BNP, ET-1 and norepinephrine according to NYHA and systemic ventricular function class (all ANOVA $p<0.001$ and <0.05 respectively). Even asymptomatic patients had evidence of significant neurohormonal activation. In contrast there was no direct relationship between the 4 anatomic subgroups and any of the neurohormones studied (all ANOVA $p>0.2$). Neurohormonal activation related to cardiothoracic diameter, atrial volume and peak oxygen consumption in a manner indistinguishable from chronic heart failure.

Conclusions: Neurohormonal activation in adult congenital heart disease bears the hallmarks of chronic heart failure, relating to symptom severity and ventricular dysfunction and not to anatomical substrate. Neurohormonal antagonism across this large and anatomically diverse population should be considered.

CONGENITAL HEART DISEASE: METABOLISM AND ARRHYTHMIAS

3289 Management of junctional ectopic tachycardia by hypothermia after cardiac operations in infants

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Background Junctional ectopic tachycardia (JET) is a postoperative complication after repair of congenital heart disease, especially in infants. The high ventricular rate, the poor response to conventional antiarrhythmic drugs and the resistance to electrical cardioversion make it be associated with a high morbidity and mortality. The purpose of this study was to assess the safety and efficacy of moderate hypothermia in the treatment of postoperative JET in infants.

Methods The case notes of 12 infants (9 females, aged between 8 days and 7 months) with postoperative JET, diagnosed according to established criteria, who were treated with surface cooling by placing ice bags on the child's body surface, were reviewed. The patients were sedated, mechanically ventilated, and paralysed. Moderate hypothermia was defined as rectal temperature between 32° and 35°C. Atrial pacing was used as an adjunct to hypothermia, in order to restore atrioventricular synchrony.

Results Mean interval between diagnosis of JET and initiation of hypothermia was 1.5 ± 0.5 hours (mean ± SD). Moderate hypothermia was achieved in 10 patients. Hypothermia led to a reduction in heart rate in all patients within four hours (from 189 ± 17 to 166 ± 16 beats/minute, $p<0.001$), with rises in systolic blood pressure (from 69 ± 11 to 78 ± 21 mmHg, $p=0.14$) and hourly urine output (from 3.3 ± 2.3 to 5.0 ± 2.1 cc/kg/minute, $p=0.015$), and reduction in central venous pressure (from 14.3 ± 4.8 to 11.3 ± 3.3 mmHg, $p=0.027$). No direct adverse events were noted. Cooling was maintained for a period of 36 to 144 hours (74 ± 42 hours). All patients but one survived and, after a follow-up period of 15 ± 12 months, they stay alive and without neurological deficits.

Conclusions Early institution of moderate hypothermia, with atrial pacing as a complementary measure, was a safe and efficient method to control ventricular rate and improve haemodynamic condition in infants with postoperative JET.

3290 Long QT syndrome with syndactyly, a novel highly malignant variant of inherited arrhythmias in the normal heart

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The association between Long QT Syndrome (LQTS) and syndactyly defines a distinct clinical entity (LQTS-syn). Seven cases with this variant of LQTS have been reported and they were all sporadic forms leading to the suggestion that the disease is due to de novo mutations. Here, we report 5 patients affected with LQTS-syn including the first evidence of a familial form of this syndrome. In all cases cutaneous syndactyly involving the third to the fifth fingers was identified at birth. Markedly prolonged QT was evident (560±50 ms) and it was associated with episodes of functional 2:1 AV block in the majority of patients. In three out of five patients macroscopic T wave alternans was observed at Holter monitoring. Beta blocker therapy was implemented in all patients. After a follow up of 26±23 months 3/5 (60%) patients experienced cardiac events (two of them died after elective surgery). Given the unfavourable outcome of the previously reported cases despite beta-blockers and pacing, we implanted an ICD in the two living patients with QTc exceeding 600ms (age at implant 6 and 1 year, respectively). Eight months after implantation, the one year old child experienced a cardiac arrest while playing. The other patient has remained asymptomatic. We performed molecular screening on LQTS related genes and failed to demonstrate the presence of mutations in all probands. Based on the evidence of LQTS-synd in a female patient, the X-linked pattern of inheritance appears unlikely. On the other hand the presence of a family with two affected children and apparently unaffected parents supports the view that this variant may be inherited as an autosomal recessive trait. It is concluded that LQTS with Syndactyly is a clinically and distinct disease characterised by marked prolongation of QT interval frequently associated with T wave alternans and functional AV block. This variant of LQTS is highly malignant with inadequate response to beta-blockers: ICD should be considered in these patients.

3291 Novel mutation in the N-terminus of HERG channel causes long QT syndrome 2 with a marked variation in clinical phenotype

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Background: HERG encodes for an alpha-subunit of a voltage-gated rapidly activating delayed rectifier potassium channel (IKr). HERG exhibits two distinct and physiologically significant gating characteristics: rapid inactivation and slow deactivation. Mutations in HERG cause LQTS subtype 2 (LQT2). The clinical phenotype of LQT2 patients is due to distorted myocardial repolarization and varies markedly within affected families. HERG channels are also molecular targets for widely used pharmacological agents.

Findings: We report on a large LQTS family. Three patients died suddenly in distinct circumstances at the age of 20,22 and 23 years, one patient, who was diagnosed earlier with "epilepsy", experienced cardiac arrest but was succesfully resuscitated and one patient developed torsades de pointes evoked by the combined intake of grapefruit juice and antifungal medication. Seven family members with lenghtened QT-interval on ECG are asymptomatic while on beta-blocker therapy. Mutation analysis (Denaturing High Performance Liquid Chromatography – D-HPLC) was performed and revealed an amino-acid change from lysine to glutamic acid at codon 28 of the HERG gene (K28E). All phenotypically affected patients carry this mutation. The mutation was introduced in the HERG cDNA using PCR overlapping fragments. HEK-293 cells were transiently transfected through the lipofectamine method with mutant channels and wild-type channels. GFP was co-expressed. Whole-cell patch-clamp experiments are being done and pharmacological challenges with IKr blockers are planned.

Conclusions: A novel mutation in the HERG gene has been isolated in a large LQTS family. The K28E mutation is located in the cytoplasmic amino (N)-terminus of the HERG channel. This terminus, containing a PAS domain, controls deactivation, by tightly associating with the body of the K^+ channel. There is a strong belief that the in vitro study of the K28E mutation will further explain the important regulatory role of the N-terminus in HERG channel gating. More-over the use of HEK-293 allows to perform pharmacological challenges with IKr blockers in contrast to transfections in Xenopus oocytes. This study will probably render more pathophysiological insights in acquired lengthening of the QT-interval, which predisposes to dangerous arrhythmias as shown in one of our patients.

Five patients in this LQT2 family have a severe phenotype and seven patients are asymptomatic. These findings stress again the variety in clinical presentation in the LQTS and points to the important role of modifier genes.

3292 High-Incidence of misdiagnosed epilepsy in children with syncope caused by malignant ventricular tachyarrhythmias

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Background: The vast majority of syncopal attacks in children are related to cardiogenic disease, however most cases are first referred to a neurologist. Consequently patients reach the cardiologist already under anticonvulsive therapy.

Methods: Out of 2.000 ambulatory 24-Holter recordings performed from 1998 to 2000, we analyzed the data of 610 pediatric patients. From these, we selected the malignant ventricular electrical rhythm disturbances which could be potentially responsible for syncope or sudden death. The data included: 1. History of previous use of anticonvulsive therapy. (AntiConvT). 2. Familial sudden death (SD) caused by "epilepsy" (FamEpSD). 3. Syncope Characteristics (SyncChar).Results: The study group included 21 patients, 12 females and 9 males, with a mean age of 11,7 ± 5,3 years. Twelve patients had Congenital Long QT Syndrome, among these, 05 (42%) had a history of syncope, 2/5 (40%) used AntiConvT, 1/5 (20%) had FamEpSD and all had undefined SyncChar. Seven patients had catecholaminergic bi-directional ventricular tachycardia, all with a history of syncope (100%), use of AntiConvT was noted in 3 (43%), FamEpSD in 2 (28.5%) and SincCar related to exercise or stress in all. Two patients presented the short coupled variant of torsade des pointes, both with syncopal episodes (100%), without previous use of AntiConvT, no FamEpSD or undefined SyncChar. Incidence of SD or aborted cardiac arrest was 21%, all under 12 years of age. Conclusions: 1. Pediatric patients with syncopal attacks and lethal arrhythmias, have a significant risk of being misdiagnosed as Epilepsy and treated with an anticonvulsive drug, 2- Primary prevention becomes necessary and includes an interaction among pediatric cardiologists and neurologists.

3293 High incidence of appropriate and inappropriate ICD therapies in children and young adults

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Background: Appropriate and inappropriate ICD therapies have a major impact on morbidity and quality of life in ICD recipients, but have not been systematically studied in children and young adults during long-term follow-up.
Methods: Incidence, reasons and predictors of ICD therapies were analyzed in 20 young patients (age: 16±6 years, congenital heart defect: 11 Pt, LQT-Syndrome: 4 Pt, idiopathic VF: 2Pt, ARVD: 1 Pt, ICM: 1 Pt, HOCM: 1Pt) after epicardial ICD implantation in 6 and transvenous implantation in 14 Pt during 51±31 months [18-132].
Results: There was a total 239 ICD therapies in 17 Pt (85%) with a therapy rate of 2.8 per patient-years of follow-up. 127 ICD therapies (53%) in 15 Pt (75%) were categorized as appropriate and 112 therapies (47%) in 10 Pt (50%) as inappropriate with a rate of 1.5 appropriate and 1.3 inappropriate ICD therapies per patient-years of follow-up. Time to first appropriate therapy was 16±18 months, caused by VF in 29 and VT in 98 episodes. Termination was successful by ATP in 4 (3%) and by shocks therapy in 123 episodes (97%). Time to first inappropriate therapy was 16±17 months, caused by AF/AFL or sinus tachycardia in 77 (69%), T-wave oversensing in 19 (17%) and electrode defect in 16 episodes (14%). Inappropriate therapies were shocks in 87 (78%) and only ATP in 25 episodes (22%). No clinical variable (age, gender, repaired congenital heart disease, history of supraventricular tachycardia, epicardial electrode system) could be identified as predictor of either appropriate or inappropriate ICD therapies.
Conclusions: There is a high rate ICD therapies in young ICD recipients, the majority of which occur during early follow-up. The rate of inappropriate therapies is as high as 47% and is caused by supraventricular tachycardia and electrode complications in the majority of cases.

3294 Pre-natal exposure to carbon monoxide delays post-natal electrophysiologic maturation of rat ventricular myocytes: a link to SIDS?

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Maternal smoking during pregnancy and prolongation of the QT interval on the electrocardiogram in the first weeks of life are considered as risk factors for Sudden Infant Death Syndrome (SIDS). In animal models, prenatal exposure to carbon monoxide (CO), a major component of cigarette smoke affects postnatal development of several organs; no data are available concerning cardiac electrophysiological development. In neonatal rat myocytes, the physiological cell growth is accompanied by a significant reduction of the action potential duration (APD), the cellular determinant of QT interval, due to an increased expression of the transient outward current. The aim of this study was to compare cell electrophysiological maturation in male Wistar rats born from mothers exposed to 0 (CTR) or 150 ppm CO during pregnancy, resulting in blood carboxyhaemoglobin levels comparable to those found in human smokers.
Methods: Action potential and ionic currents were measured in patch-clamped myocytes isolated at different ages after birth (1, 2, 4 and 8 weeks). Cells were superfused with a normal Tyrode's solution (to measure action potential, AP) or appropriately modified Tyrode's solutions (to measure transient outward current, TO and the L-type calcium current, CaL).
Results: Postnatal increase in cell size was similar in both groups; however, differences were observed in the electrophysiological parameters during growth. APD measured at -50 mV (APD50) progressively decreased in CTR from 131±24 ms at 1 week (n=14) to 78±8 ms at 4 weeks (n=14) and 67±7 ms at 8 weeks (n=10). This process was delayed in CO: at 4 weeks, APD50 remained significantly prolonged (148±24 ms, n=13) versus 4-week old CTR ($p<0.02$) and progressively shortened up to 92±12 ms (n=10) at 8 weeks. The ionic basis of APD shortening involved both calcium and potassium currents abnormalities. At 4 weeks, the density of CaL was significantly ($p<0.02$) higher in CO than in CTR (21±2 pA/pF, n=17, vs. 16±2 pA/pF, n=22) and normalized thereafter (at 8 weeks: 15±1 pA/pF, n=28 in CTR and 14±1 pA/pF, n=18 in CO). TO density progressively increased in CTR (in pA/pF, from 4±1 at 1 week to 13±2 at 4 weeks and 14±2 at 8 weeks, $p<0.01$), but it remained lower in CO at 4 and 8 weeks (respectively, 7±1 pA/pF, n=22, $p<0.01$ vs. 4-week old CTR; 8.5 pA/pF, n=13, $p<0.01$ vs. 8-week old CTR).
Conclusions: Prenatal CO exposure affects the physiological shortening of APD, thus favoring QT prolongation and related arrhythmias and possibly contributing to SIDS occurrence.

INTERVENTIONAL CARDIOLOGY IN CONGENITAL HEART DISEASE

3295 Long-term outcome of balloon aortic valvuloplasty in infants and children

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Objective: Evaluation of clinical outcome after balloon aortic valvuloplasty (BAV) in infants and children.
Methods: Retrospective analysis of patient files in a tertiary referral center.
Results: Since 1986 BAV was used as primary treatment in all consecutive patients (pts) with severe aortic valve stenosis (VAS) and in pts with residual stenosis after surgery. In a 15 year period 82 pts (58 boys, 24 girls, age range 3 days-15 yrs) underwent BAV for VAS. 38/82 pts were infants. 18/82 pts underwent earlier surgical valvulotomy. Follow up (mean 7 yrs) was complete in 80 pts. Mortality concerned 8 pts, of whom 7 during infancy. Two infants of these died during the intervention, caused by aortic regurgitation in one and arterial bleeding in the other. The other 6 pts died because of cardiac failure in 4, endocarditis in one and acute arrhythmia 11 yrs after BAV in one pt refusing surgery. Re-interventions were necessary in 40 pts during follow up: repeat BAV in 11 pts, surgical aortic valvulotomy in 3 and valve replacement in 26 pts. The indication for valve replacement (pulmonary autograft) in these 26 pts was valve stenosis in 44%, regurgitation in 33% and a both stenosis and regurgitation in the remaining pts. Of the 11 pts that underwent a repeat BAV 4 required subsequent valve replacement during follow up. At 5 yrs follow up 53% of pts were free from any re-intervention. During the study period up endocarditis occurred in 4 pts which was fatal in one.
Conclusion: In infancy mortality and the need for re-interventions after BAV for VAS is considerable. After infancy BAV for VAS is a successful and low risk therapy at longer term, postponing surgical intervention in the majority of pts.

3296 Long-term results of percutaneous balloon dilation for discrete subaortic stenosis. A 17-year study

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Transluminal balloon dilation (TBD) for thin discrete subaortic stenosis (DSS) is a useful alternative to surgical therapy. Better initial results are observed in patients with larger aortic annulus and a membrane further away from the valve. However, given the progressive nature of the disease, the long-term efficacy of this treatment remains unknown. This 17-year study describes the findings obtained in 66 patients with isolated DSS who underwent percutaneous TBD and were followed-up for a mean period of 7±5 years (range 2 months-17 years). The mean age at treatment was 17±15 years (range 2 to 56). The procedure evolved through time but was always oriented to transcatheter tearing of the membrane. One patient 56 years old died after emergency surgery for inferior wall rupture during dilation manoeuvres (1.5%). Immediately after treatment, the subvalvular gradient decreased from 67±27 mmHg to 17±11 mmHg ($p<0.001$). No significant progression of aortic regurgitation was observed after treatment; in 7 (11%), aortic regurgitation even decreased after treatment. None of the patients developed mitral insufficiency. Sixty-five patients were followed up closely and had serial echo-Doppler or hemodynamic studies. After a mean follow-up time of 7±5 years, 1 patient had a non cardiac death (1.6%), 8 pts (12%) developed restenosis (loss of 50% of initial gain), 2 (3%) progressed to muscular obstructive disease and one developed a new obstructive distant membrane. The age at treatment was significantly lower in patients who developed restenosis as compared with that from patients restenosis-free (7±4 vs 19±14 years, $p<0.001$). To date, no patient older than 13 years has had restenosis. Nine pts were redilated at a mean follow-up time of 4±1 years after first treatment. The peak gradient decreased again from 74±30 mmHg to 22±14 mmHg ($p<0.001$) and none had progression of aortic regurgitation. Two patients (3%) were surgically operated 9 months and 5 years after first treatment. Fifty-five patients (83%) remain free of re-dilation and/or surgery without progression of aortic insufficiency or muscular obstructive disease. The mean last residual gradient, either hemodynamic or Doppler, was 28±11 mmHg at a mean follow-up of 7±4 years.
Conclusions: TBD is an effective modality of treatment in patients with isolated thin DSS, mainly in those older than 13 years of age. More than 80% of patients persist with the initial benefit at long-term follow-up (mean 7 years). Redilation, when needed, is similarly effective to first-dilation and seems to provide persistent relief.

3297 Percutaneous closure of large PDA (diameter > 2.5 mm) with the ADO. Comparisons with the Rashkind, buttoned devices and coils in 116 patients

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Design of previously employed devices is not ideal for transcatheter closure of moderate-to-large patent ductus arteriosus (PDA), and their use has been associated with several drawbacks.

Method and Results: This study was performed to compare results of transcatheter closure of PDA (diameter above 2.5 mm) using the Amplatzer Duct Occluder (ADO) and previous occluders. One hundred and sixteen patients (77 females, 39 males) underwent PDA closure with several devices: Rashkind double umbrella (n=23, group I), Sideris buttoned device (n=39, group II), detachable Cook coil (n=17, group III), and ADO (n=37, group IV) at a mean age of 74 ± 129 months (weight: 18.9 ± 15.5 kg). Duct diameter was 3.8 ± 1.22 mm. Implantation succeeded in all but 9 (3 in group I, 2 in group II, 3 in group III, and 1 in group IV). Time of fluoroscopy was shorter and full occlusion better on angiography (64%) in group IV despite larger ducts (respectively $p<0.0001$, $p=0.0003$ and $p=0.0015$). Complications included embolization (n=2, 1 in group I and 1 in group III) and hemolysis (n=3, 2 in group III and 1 in group IV). During follow-up, 12 patients had a second procedure because of residual shunting (5 in group I, 6 in group II, and 1 in group III). Complete occlusion was achieved earlier after implantation (mean 2.6 months, $p=0.0002$) and rate of complete occlusion was better in group IV (97%, $p=0.025$).

Conclusions-Transcatheter closure of PDA with the ADO is an effective and safe technique which provides better results than previous occluders. It could be highly recommended for closure of large ducts (> 2.5mm).

3298 Single center experience of transcatheter closure of atrial septal defects using different devices

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Percutaneous closure of secundum type atrial septal defects (ASD)as therapeutic approach is widely used not only in the pediatric patient group. A number of different technical specifications have been used. We report our single centre experience in a mixed population with the two most commonly used systems Amplatzer septal occluder (ASO) and Cardio Seal/Cardio Seal Starflex (CS/CSSTF).

In a 4 year period (1997 to 2001) 93 pts were scheduled for the procedure -aged 2 -71y, weight 10-91kg, 38% being <18 years and 15% > 50y. The procedure was performed under general anesthesia in all children and most adults, using TEE in all. Anticoagulation -heparine- was given for the procedure, antiplatelet therapy for the following 6 months. In 13 pts the procedure was stopped after balloonsizing. 81 devices were implanted, in one girl two defects were closed with two devices in the same session (CS).

There were 29 pts treated with CS/CSSTF and 51pts with ASO. We found no significant differences between the ASO and CSSTF group, although Qp:Qs and ASD- size were larger in the ASO group.There was also a tendency of smaller rims at the aortic border of the ASD in the ASO group. Procedure time und radiation time showed no significant difference (4.5 - 37 min, mean 10.2).

Successfull implantation was possible in all pts when attempted, in those rejected, the single defect was too large in comparison to the intraatrial septal length, and/or had no sufficient rim for either device. In the setting of multiple defects (3x) there was either no place for mutliple devices or insufficient rims too.

There was no early or late embolisation. We encountered only one serious complication. In a 4 year old girl with insufficient systemic anticoagulation a cerebral infarction with hemiparesis occurred within the first 12 hours after the procedure. Symptoms resolved qucikly and are almost gone three years after the implantation.

On follow up with TTE and TEE there are three trivial residual leaks;in 1 adult the initially well positioned device showed diffrent psoition and significant shunt at the 1 year followup.

CS/STF-devices are mainly used in smaller pts with defects upto 20 mm, although we also use now the 6-arm device where defects up to 26 mm can beclosed.ASO- devices were implanted also in defects exceeding even 30 mm.

In our experience ASD's in all ages can be addressed safely with transcatheter closure when the appropriate device for the pt and defect size is selected.

3299 Incidence and clinical outcome of thrombus formation on ASD and PFO closure devices in 900 consecutive patients

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Purpose: The purpose of this study was to investigate incidence, morphology and clinical course of thrombus formation on atrial septal defect (ASD) and patent foramen ovale (PFO) closure devices.

Methods: Between August 1992 and January 2001 in 900 consecutive patients transcatheter closure of a patent foramen ovale (n=537) or an atrial septal defect (n=363) was performed. Routine transoesophageal echocardiography (TEE) was performed after 2-4 weeks and 6 months.

Results: Thrombus formation in the left (n=11) or the right atrium (n=6) or both (n=3) was found in 5/360 ASD patients (1.4%) and in 15/531 (2.8%) PFO patients. This was observed after 2-4 weeks in 14, after 6 months in 3, after 1 year in 2 and after 5 years in 1 patient. The diameter of the thrombus varied from 5 to 30 mm (12 ± 7). After 4 weeks the TEE revealed thrombus formation in 7% on the CardioSEAL, the STARFlex and the PFO-Star occluder, in 4% on the ASDOS occluder, in 1% on the Helex occluder and in 0% on the Sideris and the Amplatzer occluder. The difference between the Amplatzer on one hand and the CardioSEAL, the STARFlex and the PFO-Star occluder on the other hand was significant ($p < 0.05$).

Prethrombotic disorders were found in 2 PFO patients (thrombocytosis and hyperactivity of Factor VIII), post procedure atrial fibrillation in 4, persistent atrial septal aneurysm despite device implantation in 4, device arm fractures in 3 (N.S.).

Three minor strokes and one TIA occurred. In 17/20 patients the thrombus resolved following anticoagulation therapy with heparin or warfarin. In 3/20 patients the thrombus had to be removed surgically.

Conclusion: The incidence of thrombus formation on closure devices is low. In most of the patients the thrombus resolves under anticoagulation therapy without clinical consequences. Surgery is rarely needed and should not be recommended generally.

3300 Right ventricular size after device closure of atrial septal defects – Serial changes and factors affecting them

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Introduction: Right ventricle (RV) will remodel and decrease in size when the volume overload due to atrial shunting is abolished. The time course of these changes and factors affecting the changes were studied in patients undergoing device closure of atrial septal defect (ASD) where the effect of anaesthesia and surgery are absent.

Methods: In 28 patients (17 females), RV size was measured before and 2 days (2d) after successful closure of ASD with Amplatzer device and at follow-up of 3 months (3m) and 1 year (1y).

Results: Mean age was 22.3±17 years and mean body surface area 1.31±0.32 m^2. Mean left to right shunt (Qp:Qs) was 2.08±0.53. RV dimension (RVD, in mm) before closure (RVD-pre) was 28.6±8.2. RVD 2d after closure (RVD-2d), at 3m follow-up (RVD-3m) and at 1y follow-up (RVD-1y) are shown in table 1. The decrease in absolute RVD, decrease in indexed RVD and percentage decrease in RVD are also shown in table 1. Significant correlations of Qp:Qs with decrease in RVD were seen for values at 2d and at 1y follow-up: (i) with absolute decrease at 2d: $r=0.72$, $p<0.005$; absolute decrease at 1y: $r=0.7$, $p<0.05$; (ii) with decrease in indexed size at 2d: $r=0.7$, $p<0.03$; decrease in indexed size at 1y: $r=0.78$, $p<0.02$; (iii) with percentage decrease at 2d: $r=0.69$, $p<0.002$; percentage decrease at 1y: $r=0.8$, $p<0.01$. There was a weak correlation of age with decrease in RVD at 2d: $r=0.49$, $p<0.008$.

	2 days	3 months	1 year
RVD after closure of ASD*	24.8±6.3	20.0±4.1	18.6±4.9
Decrease in absolute RVD	3.8±2.7	4.2±3.3	0.75±0.7
Decrease in indexed RVD	2.7±1.7	3.0±2.1	0.5±0.5
Percentage decrease in RVD	12.3±6.7	16.6±9.5	4.0±4.0

* $p<0.03$ between RVD-pre and RVD-2d, $p<0.05$ between RVD-2d and RVD-3m and $p<0.02$ between RVD-3m and RVD-1y

Conclusions: There is an immediate and a delayed decrease in RV size after device closure of ASD. The decrease is significantly related to the magnitude of the shunt prior to closure and weakly to the age of the patient. The early changes in RV size (unaffected by the morbidity of anaesthesia and surgery) are greater than the decrease in RV size at 1 year following ASD closure. Larger studies are required to clarify this.

PROGNOSIS OF ACUTE MYOCARDIAL INFARCTION: REGISTRIES VERSUS STUDIES

3301 Outcome of myocardial infarction in the unselected population is vastly different from samples of eligible patients in large-scale clinical trials

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Several large scale clinical trials of fibrinolysis in ST-elevation myocardial infarction (MI) have repeatedly demonstrated an impressively low mortality - 6% at 30 days and 9-10% at 1 year. It has, however, been questioned whether these results are representative for unselected patient populations.

Methods: The ASSENT-2 (A2) trial randomised ST-elevation MI patients to fibrinolytic treatment with tPA or TNK-tPA without any difference in outcome. Out of the 17005 patients 1070 were recruited in Sweden out of which 753 in hospitals simultaneously recording all CCU admissions in the national CCU registry RIKS-HIA. During the period for A2 recruitment another 2977 patients (Non-A2) with fibrinolytic treatment for acute MI were recorded in the RIKS-HIA. The data obtained in the RIKS-HIA registry and 1-year outcome, based on matching with the National registry for death, were used for the comparisons.

The Non-A2 population was significantly older and contained more women, diabetes mellitus, previous MI and used more anti-thrombotic and diuretic medication than the A2 patients. Further, in multivariate analysis, participation in the ASSENT-2 study was significantly ($p<0.001$) associated with improved 1-year survival adjusting for age, gender, diabetes mellitus, previous MI, congestive heart failure and medication at entry.

Results:

Results: Death at 1 yr	n/n	A2	Non-A2	p
Total	753/2977	9.0%	20.0%	<0.001
Age <65 years	314/1035	1.9%	5.2%	0.012
Age 65 - 75 years	260/861	7.3%	16.0%	<0.001
Age >75 years	179/1081	24.0%	37.4%	<0.001

Conclusion: The unselected acute MI population has considerably worse outcome than acute MI patients eligible for clinical trials. The natural course and the effects of different treatments in acute MI needs to be monitored also in broader patient populations than usually included in clinical trials.

3302 Study results did not represent real-life practice – Data from GUSTO-5 and ACSIS-2000

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Among the 16,588 patients (pts) who participated in GUSTO-5, 1973 were recruited in Israel. The study did not show a significant mortality difference between the two arms of the study (5.6 vs. 5.9%). The low 30-day mortality was suggested as the reason for the lack of difference between the two study groups. A national survey on AMI, ACSIS-2000, was performed during the conduction of GUSTO-5 in Israel and included 1,112 pts with ST elevation MI, of whom 473 (43%) were treated with thrombolysis. Two hundred and fifty pts were recruited to GUSTO-5 and 220 received routine thrombolysis in the same CCUs which recruited pts to GUSTO-5. The mean age of GUSTO-5 pts was lower (59 yrs) than that of patients included in the survey (controls) (62 yrs; $p<0.05$). The control group also included more diabetics (35%) and hypertensives (42%) than counterparts (23 and 32% respectively; $p<0.05$ for each). More pts included in GUSTO-5 presented with typical symptoms (96%) vs. controls (89%; $p<0.05$), while the latter group were more often in Killip class >2(18%) than the GUSTO-5 group pts (12%; $p<0.05$). In the GUSTO-5 group, all pts received tPA while among the control group, 82% received STK. Aspirin and beta-blockers were equally given to both groups. Coronary angiography was performed in 59% of GUSTO-5 cases versus 50% in the control group. The median time from pain onset to thrombolysis was similar in GUSTO-5 (165') and the control group (157'). Thirty-day mortality was 4.1% in the GUSTO-5 group versus 10.2% among controls ($p<0.05$). This study showed that only 43% of STE MI were treated with thrombolysis and only 50% of pts eligible for thrombolytic therapy were included in the trial. Pts included in GUSTO-5 exhibited a lower risk profile than counterparts treated with standard thrombolysis and therefore had different outcomes. This study emphasizes the importance of maintaining a registry when clinical studies are performed.

3303 Changes in in-hospital management and outcome of acute myocardial infarction in the late 1990s: the nation-wide French 1995 and 2000 registries

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The hospital management of patients with acute myocardial infarction (AMI) has changed considerably in the last decade. In order to assess possible differences in "real world" management and outcome of AMI in the late 1990s, we conducted 2 nation-wide registries using a similar methodology in intensive care units representing more than 3/4 of all French ICUs in November 1995 and November 2000. A total of 2563 patients with AMI < 48 hours from symptom onset were included in 1995, and 2320 patients in 2000. Patients admitted in 2000 were significantly younger (65.4 ± 14 vs 66.6 ± 14 years, $p<0.05$), but the sex ratio and prevalence of risk factors were similar. Previous medical history was also similar (prior MI: 16% vs 18%, CHF: 9% vs 6%; stroke: 7% vs 5% and peripheral artery disease: 10% vs 9%). Intravenous thrombolysis was used less often in 2000 (24% vs 32%), while the use of early PTCA was more frequent (32% vs 13%); overall reperfusion therapy by either thrombolysis or PTCA was used as often in 2000 (43% vs 43%). The use of reperfusion therapy decreased with increasing age in both cohorts. In the younger patients (< 50 years) the use of early PTCA was half in 1995 (21%) compared with 2000 (45%); in older patients, also, early PTCA was used much more frequently in 2000 than in 1995 (patients 70–79 years: 25% vs 11%; patients 80 years and older: 12.1% vs 4.6%). Cardiogenic shock developed in a similar proportion of patients in the 2 cohorts (6.6% vs 7.0%) and ventricular fibrillation was also as frequent in the 2 cohorts (3.8% vs 3.5%). Five-day mortality, however, was lower in 2000 than in 1995 (5.8% vs 7.7%, $p = 0.01$), a difference that remained significant in multivariate analysis ($p<0.03$) The other independent factors of 5-day mortality were age, diabetes mellitus, previous stroke, and anterior location of MI; use and modality of reperfusion therapy were not significantly and independently related to early mortality.

Conclusion: patients admitted for AMI in France are sligthly younger in 2000 than in 1995; the use of reperfusion therapy is similar, with a dramatic shift from thrombolysis to PTCA. Early mortality has continued to decline from 1995 to 2000, but there is no evidence that this change is related to the changes in mode of reperfusion therapy.

3304 Predictors of in-hospital mortality in the global registry of acute coronary events (GRACE)

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Background: Specific pharmacologic (e.g. glycoprotein IIb/IIIa inhibitors) and interventional strategies (revascularization), have most benefit in high risk acute coronary syndromes (ACS) patients. However, recent registry data suggest that clinical practice is not always based on trial evidence or current treatment guidelines. Robust and clinically applicable risk models are needed to guide routine practice, but prior risk models have been derived from restricted or trial populations and may be less widely applicable.
Methods: GRACE is the largest multi-national registry including patients with the full spectrum of ACS. We developed a multivariable logistic regression hospital death-prediction model in 11,380 patients (509 in-hospital deaths) and validated the model in a prospective cohort of 3,972 patients and also in 12,142 patients from the GUSTO IIb trial.
Results: Eight independent risk factors accounted for 90% of predictive information for the risk of in-hospital death in the model (Table). Two new independent predictors were identified: resuscitated cardiac arrest and serum creatinine. The model demonstrated excellent discriminant ability with a C statistic of 0.83 for the derived data set, 0.84 for the confirmatory data set and 0.79 for the external GUSTO IIb database.

Risk factors for in-hospital death

Risk factor	OR	Grace score
Resuscitated cardiac arrest	4.3	+39
ST-deviation	2.4	+28
Killip class	2.0 per class	0 - 59
Age	1.7 per 10 yrs over 30	1 - 100
Elevated initial cardiac markers (CRP, Troponin)	1.6	+14
Systolic BP	1.4 per 20 mmHg under 200	0 - 58
Heart rate	1.3 per 30 bpm over 50	0 - 46
Creatinine	1.2 per mg/dl under 4	0 - 28

Independent risk factors for in-hospital death (cumulative score predicts risk of death)

Conclusion: The GRACE registry has provided a robust risk model for the hazard of in-hospital death, regardless of whether the patient presents with ST-elevation MI, non-ST MI or UA. The GRACE cumulative score can be used in a nomogram or personal digital assistant (PDA) to predict death and hence guide clinical practice.

3305 Targeting improved adherence to the ACC/AHA guidelines for the management of non-ST-segment elevation acute coronary syndromes

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Background: Despite publication of the revised ACC/AHA guidelines for the management of non-ST-elevation acute coronary syndromes (NSTE ACS) in 2000, implementation of the treatment recommendations from the guidelines in clinical practice has not been well-characterized.
Methods: The CRUSADE national quality improvement initiative has been developed to encourage adherence to the ACC/AHA guidelines for the management of high-risk patients with NSTE ACS in U.S. hospitals. A unique collaboration of Cardiologists and Emergency Medicine physicians has been established for CRUSADE to improve early risk stratification strategies and the quality of hospital-based care provided to patients with NSTE ACS.
Results: Since December, 2001, a total of 892 patients have been included in CRUSADE. Of these patients, 50.1% presented with ST-depression, 70.9% presented with elevated cardiac markers (CK-MB or Troponin I or T), the median age was 69 years (57,78 years), and 39.8% were female. Baseline use of acute and discharge therapies recommended by the ACC/AHA guidelines is displayed in the table. By August, 2002, projections indicate that approximately 8000 patients will be included in the CRUSADE database.

Acute and Discharge Medications

Medications*	Acute Use (1st 24 hours)	Discharge Use
Aspirin	89.6%	86.4%
Beta-Blockers	74.4%	82.7%
Heparin	83.7%	–
Glycoprotein IIb/IIIa Inhibitors	34.3%	–
ACE-Inhibitors	–	54.9%
Statins	–	56.2%

* Medication use reported for eligible patients without specific contraindications according to recommendations from the ACC/AHA guidelines; GP, glycoprotein;

Conclusions: Preliminary results from the CRUSADE quality improvement initiative demonstrate suboptimal adherence to the ACC/AHA guidelines for the management of NSTE ACS. These data provide targets for interventions designed to improve the quality of care for high-risk patients with NSTE ACS.

3306 Sustained prognostic value of TIMI risk score in acute coronary syndromes

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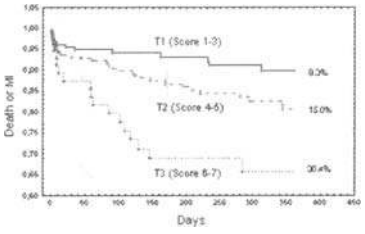
Background: TIMI Risk Score is a simple clinical score for short-term risk stratification and for therapeutic decision-making in patients (Pts) with non-ST-elevation acute coronary syndromes (ACS). Nevertheless, its value for long-term prognosis is unknown.
Objective: We sought to evaluate the prognostic value of TIMI Risk Score at 1 year after ACS.
Methods: We studied 433 consecutive Pts, admitted to our CCU with ACS (mean age 64±11 years, 21% female, 67% with unstable angina). The 7 variables of the TIMI Risk Score were applied at admission. Prognostic value was evaluated by the combined endpoint of death or myocardial infarction (MI) at 30 days and at 1 year.
Results: The incidence of death/MI at 30 days follow-up was 4.5% for Pts with TIMI Risk score 1-3 (T1, n=157), 6.8% for Pts with TIMI Risk score 4-5 (T2, n=220) and 14,3% for TIMI Risk score 6-7 (T3, n=56). Between 30 days and 1 year, the incidence of the combined endpoint was 4% for T1, 8.8% for T2 and 16.7% for T3 and at 1 year 8.3%, 15% and 30.4% respectively. The cumulative incidence of death or MI at 1 year was significantly higher in T2 or T3 versus T1 (p=0.006).



Cumulative incidence of death or MI.

Conclusion: Besides being a good prognostic indicator at 30 days, the TIMI Risk Score seems to keep it's prognostic value at one year follow-up.

PERICARDITIS

3307 Is two-dimensional echocardiography sensitive and specific enough to diagnose cardiac tamponade?

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Echocardiographic prediction of cardiac tamponade is controversial. The aim of the present study was to evaluate sensitivity and specificity of two-dimensional (2D) echocardiographic signs of cardiac tamponade in comparison to the invasive hemodynamics.

Methods: In 50 pts with large pericardial effusions (PE) (58% males, age 54.2±9.6 yrs, PE> 2 cm anteriorly) echocardiography was performed immediately before cardiac catheterization and pericardiocentesis. Diagnosis of cardiac tamponade was established only if both clinical (jugular venous distention, tachycardia, hypotension, pulsus paradoxus) and hemodynamic signs were present (elevation and equilibration of intrapericardial and right atrial (RA) pressures).

Results: According to the clinical and hemodynamic criteria 8/50 pts (16%) undergoing pericardiocentesis for large symptomatic PE had cardiac tamponade. Average volume of PE evacuated by pericardiocentesis in pts with tamponade was larger but not significantly different in comparison to pts without tamponade (725±344 ml vs. 649±421 ml; p=0.317). Among the investigated 2D-echocardiographic parameters (table) RA collapse and sustained inferior vena cava (VCI) congestion had 100% sensitivity, but low specificity. Right ventricular (RV) diastolic collapse and "swinging heart" had high sensitivity, but low specificity. In contrast, left atrial (LA) collapse was highly specific, but had low sensitivity, with a positive predictive value of 42.9%. Sudden leftward motion of the interventricular septum (IVS) was the only parameter with both high sensitivity and specificity, and the positive predictive value of 80% for the diagnosis of cardiac tamponade.

N=50 pts	RA collapse (45 pts)	LA collapse (4 pts)	RV collapse (38 pts)	Swinging heart (29 pts)	Leftward IVS motion - inspirium (10 pts)	VCI congestion (29 pts)
Sensitivity (%)	100	37.5	75	75	100	100
Specificity (%)	11.9	90.5	23.8	45.2	95.2	50
Positive predictive value (%)	17.8	42.9	15.8	20.7	80	27.4

Sensitivity, specificity, and positive predictive value of the 2D-echocardiographic signs of cardiac tamponade. RA - right atrium, RV - right ventricle, LA - left atrium, VCI - inferior caval vein, IVS - interventricular septum.

Conclusion: Leftward IVS motion in inspirum is a valuable 2D-echocardiography sign of cardiac tamponade that should be systematically investigated in patients with large PE.

3308 Effect of cardiac tamponade in left ventricular pressure volume relations in humans

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Background: In this study we use, for first time in humans, the analysis of left ventricular (LV) pressure-volume loops to estimate the influence of cardiac tamponade in LV performance. This method is considered independent from preload and afterload changes, which are extreme during cardiac tamponade.

Methods: We studied eight patients (4 men, mean age 53±6 years). All patients were free of previous cardiovascular events, with large pericardial effusion of neoplasmatic origin and were scheduled to undergo percutaneous balloon pericardiotomy. According to our protocol, we infused sucrose solution in the evacuated pericardial space (after successful percutaneous pericardiocentisis) until achievement of cardiac tamponade or strong patient discomfort. A conductance catheter was used to analyse LV pressure volume loops continuously and compute LV mechanics at baseline and after tamponade.

LV end-systolic elastance (EES), preload recruitable stroke work (PRSW), cardiac index (CI) and stroke work (SW) were derived as indexes of systolic performance while LV end-diastolic volume (LVEDV), LV end-diastolic pressure (LVEDP), LV chamber stiffness index (LVCSI) and time constant of isovolumic relaxation time (Tau) as indexes of diastolic function.

Results: Indexes of cardiac filling (LVEDV: 131.0±6.5 vs 90.4±5.0 ml, LVEDP: 10.3±1.3 vs 15.7±1.5 mmHg, $p<0.05$ for both) seemed to be impaired during tamponade as well as cardiac performance (CI: 3.5±0.3 vs 2.6±0.4 L/min.m^2, SW: 4818±626 vs 2410±283 mmHg.ml, p=0.028 for both) and LV diastolic function (LVCSI: 0.023±0.01 vs 0.037±0.02, Tau: 40.8±4.6 vs 32.3±2.8 sec, $p<0.05$ for all). In contrast, the preload-independent indexes of myocardial contractility showed no clear change at baseline and tamponade (EES: 1.08±0.19 vs 1.08±0.24 mmHg/ml, p=0.599, PRSW: 97.4±9.7 vs 94.9±14.6 mmHg, p=0.249).

Conclusions: Cardiac tamponade induces severe filling disturbances and impairs diastolic performance of the normal human heart but does not impair intrinsic myocardial contractility. Our results further support the concept that treatment should be focused in improving LV filling while the use of inotropic agents may be of limited value in the treatment of cardiac tamponade

3309 Tissue Doppler analysis of mitral annulus motion in patients with constrictive pericarditis

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Background and Introduction: Clinical diagnosis of constrictive pericarditis (CP) is difficult. It has been suggested that tissue Doppler (TVI) analysis of mitral annulus (MA) motion might be a helpful tool to differentiate CP from diastolic myocardial dysfunction. In patients (pts.) without CP, early transmitral flow velocity (E) increases with higher filling pressure (PCW), while early diastolic MA velocity (E') is reduced, resulting in a positive linear correlation between E/E' and PCW. In contrast, E' has been reported to be normal despite high PCW in CP pts. We therefore studied the relationship between E, E' and PCW in pts. with documented CP who had undergone complete invasive hemodynamic assessment.

Results: From 14 CP pts. (mean age: 56±15 years), 9 were in sinus rhythm (SR), 5 in atrial fibrillation (AF). Coexistent mitral valve stenosis (MS) or replacement (MVR) was present in 3, aortic valve replacement (AVR) in 2, a cardiac post-radiation syndrome in 1, and coronary artery disease (CAD) in 5 pt(s). Systolic LV function was normal, mean pulmonary wedge pressure (PCW) 20±5, and LV enddiastolic pressure 22±5 mm Hg. Left atrial diameter was 50±13 mm. E was 112±55 cm/s, deceleration time of E 134±36 ms, and E' 13±6 cm/s. An E' <8 cm/s was only found in the pt. with post-radiation syndrome. After exclusion of the 3 pts. with MS or MVR, the E/E' ratio and PCW showed a significant inverse correlation (E/E' = 17.0 - 0.5 x PCW; r=0.78; $p<0.01$) opposed to that described in diastolic myocardial dysfunction.

Conclusion: TVI in combination with transmitral flow analysis is a helpful new tool to differentiate severe LV filling abnormalities, independent of cardiac rhythm, and especially for the peri-operative assessment of CP. The inverse correlation of E/E' and PCW may be impaired, however, if mitral valve or myocardial disease coexist with CP.

3310 Troponin I release in idiopathic acute pericarditis: clinical and prognostic value

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Background: Acute pericarditis has been recently reported as a possible cause of non-coronary heart disease systemic release of troponin I (Tn I). The prognostic value of this observation remains unknown.

Aim: To investigate the frequence of Tn I release in patients with idiopathic acute pericarditis and to evaluate its clinical and prognostic value.

Methods: 118 consecutive cases of idiopathic acute pericarditis (age 49,2 ± 18,4; 61 males) were included from January 2000. A highly sensitive colorimetric immunoassay was used to measure Tn I (lowest measurable concentration of 0,04 ng/ml, reference interval: 0,00-0,1 ng/ml and an acute myocardial infarction -AMI- threshold of 1,5 ng/ml). Creatine Kinase(CK)-MB enzyme release was measured using an immunoinhibition assay (lowest measurable concentration of 1,0 U/l, reference interval: 0,0-6,0 ng/ml).

Results: A Tn I rise was detectable in 38 patients (32,2% of cases). The following characteristics were more frequently associated with a positive Tn I test: younger age (31,9 ± 11,4 vs 57,3 ± 15,1 years, $p<0,001$), male gender (71,0 vs 42,5%, p=0,007), ST-elevation (97,4 vs 51,2%, $p<0,001$) and pericardial effusion (86,8% vs 60,0%, p=0,007) at presentation. Among patients with a positive Tn I test a borderline or mild increase of Tn I (<0,4 ng/ml) was detected in 29 cases (group I: 76,3%) without a CK-MB elevation. An increase beyond AMI threshold was present in 9 cases with an elevated CK-MB value and echocardiographic diffuse or localized abnormal ventricular wall motion (group II: 23,7%; mean Tn I: 11,6 ± 7,8 ng/ml; mean CK-MB peak 23,6 ± 19,0 U/l). Coronary artery disease was excluded by angiography and myopericarditis was diagnosed. In group II Tn I temporal pattern was similar to that seen in AMI with levels detectable for 5-6 days while in group I the temporal pattern was shorter (2-3 days). A mean follow-up of 18 months (range 3-24 months) was performed. A similar rate of complications was found in patients with a positive or a negative Tn I test (recurrent pericarditis: 13,2 vs 15,0%; constrictive pericarditis: 0 vs 1,3%, for all p=NS; no cases of cardiac tamponade or residual left ventricular dysfunction were detected).

Conclusions: In idiopathic acute pericarditis Tn I elevation is the biochemical evidence of myocardial inflammatory damage. It is commonly associated with young age, male gender, ST-elevation and pericardial effusion at presentation and sometimes is expression of myopericarditis. Unlike acute coronary syndromes Tn I is not a negative prognostic marker in idiopathic acute pericarditis.

3311 Pericardial friction rub and effusion in pericarditis

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Background: In clinical pericarditis often a pericardial friction rub (PFR) is heard and pericardial effusion (PE) is seen on echocardiography. However, sometimes a rub is heard without PE and sometimes the other way around. The relationship between the presence of a rub and the amount of PE, if any, has hardly been studied in non-surgical pericarditis.
Methods: In 202 non-surgical patients (pts) a clinical diagnosis of pericarditis was made using history, fever, lab tests and ECG. The presence of a pericardial friction rub was scored and PE was quantitatively assessed by echocardiography: physiologic (<1mm), moderate (1-10mm), large (>10mm).
Results:

Amount of PE	Number of patients	Number of PFR	Percentage of PFR
Large	61	25	41
Moderate	48	27	56
Physiologic	93	50	54
Total	202	102	50

There was no relation between the amount of PE and the presence of PFR ($p>0.1$). However when the suspected aetiology was taken into account, there was a statistical significant relation with the presence of a rub ($p=0.0006$).
In 4/13 (31%) of pts with auto-immune disease as cause for pericarditis and in only 2/18 (11%) of pts with neoplasma PFR was heard. On the other hand, in 17/26 (65%) of post-infarction pts and in 37/64 (58%) of infectious pericarditis PFR was heard. Finally, a rub was heard in 40/78 (51%) of the idiopathic group. Taking into consideration that many cases of idiopathic pericarditis are infectious in origin and thus acute, it seems that acute pericarditis is more often correlated with a rub than the chronic one. Given the fact that fibrin deposition into the pericardial cavity is maximal at 24-48 hours after infection and that fibrinolysis occurs 6-8 days after it, we suggest that PFR is correlated with the presence of fibrin strands rather than with the amount of PE.
Conclusion: Although often suggested by clinicians, we could not identify a correlation between a PFR and the amount of PE in this large study. However, acute causes of pericarditis are more often associated with a rub suggesting that rather than the rough pericardial surfaces fibrin strings cause the rub, where they may serve as snares.

3312 Colchicine for recurrent pericarditis: influence of previous treatment with corticosteroids

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Objective: To determine the efficacy of colchicine in the treatment of recurrent pericarditis in patients refractory to corticosteroid therapy.
Background: Recurrence is one the major complications of acute pericarditis and its management is often frustrating. Corticosteroids are often attempted and frecuently unsuccessful and with significant side effects.
Methods: We included 51 patients (36 men; mean age 40.8 ± 18.7 years) with recurrent pericarditis. Prior treatment had included aspirin or other non-esteroidal anti-inflammatory drugs (n=47) and prednisone (n=29). Patients received colchicine (1-2 mg/day) for a median of 12 months (range (1-128) and were followed for a median of 36 (range 2-134 months).
Results: Patients receiving prednisone were older (42.2± 15.87 vs 39.0 ± 22.1 tears; p=0.028), had more often a secondary form of pericarditis (48.3% vs 18.2%; p= 0.027) and a greater number of relapses before colchicine was started (4.51±3.34 vs 2.54±0.67; p=0.0009). Fourteen of 29 patients who were receiving prednisone before colchicine was started (48.27%) presented with a total of 19 new recurrences. By contrast, only six of 22 patients (27.27%) who did not receive prednisone relapsed after colchicine was started (total, 7 recurrences). However, this difference was not statistically significant ($p = 0.139$). Interestingly, the benefitial effect of colchicine was greater in patients who were receiving prednisone before treatment was begun. Patients who were on prednisone before the initiation of colchicine had a significantly greater increment in the symptom-free periods during colchicine therapy (22.5±23.5 months vs. 4.6±4.7 months, p=0.0004), after colchicine was stopped (38.2±38.9 months vs. 14.4±15.7 months, p=0.0016), and for the total follow-up period (54.2±37.4 months vs. 21.3±19.2 months, $p <0.0001$).
Conclusions: Colchicine is highly effective in patients with recurrent pericarditis that are not properly controlled with corticosteroid therapy. These data suggest that colchicine should be added to succesfully withdraw corticoids and avoid adverse effects of prolonged corticosteriod therapy.

PROGNOSTIC FACTORS FOR CARDIOVASCULAR DISEASE IN HEALTHY POPULATIONS

3313 The prognostic value of the electrocardiogram in the west of Scotland coronary prevention study

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Introduction: The West of Scotland Coronary Prevention Study (WOSCOPS) recruited 6,595 men aged 45-65 years with moderate hyperlipidemia and no previous myocardial infarction (MI) who were randomised to treatment either by placebo or Pravastastin 40mg nocte. Patients were followed for a mean of 4.9 years and all events, cardiovascular or otherwise, were recorded over the period of the trial.
Aim: The objective of this sub study was to evaluate the prognostic value of the ECG with respect to the study endpoints, namely definite coronary heart disease (CHD) death and non fatal MI, as well as all cause mortality.
Methods: 12 lead ECGs were recorded using a computer assisted electrocardiograph and transmitted to a central core ECG lab. ECGs were recorded at baseline, annually and at the study run out phase. Minnesota Coding was undertaken in an automated fashion but all codes were reviewed manually. Clinical events were noted throughout the study and adjudicated by an endpoints committee. Minor ECG changes were defined as Minnesota Codes 4-2, 4-3, 5-2, and 5-3, as 4-1 and 5-1 were exclusion criteria. Ten second baseline ECG recordings were used to derive the standard deviation of normal RR intervals (SDNN) and to calculate an index of cardiac vagal tone. Left ventricular mass was calculated using an ECG based equation. Frontal plane T wave axis and the T amplitude in Lead I were also included in the analysis.
Results: An analysis of run out ECGs showed a highly significant reduction in incident T wave abnormalities (5-2) in the treated compared to the placebo group ($p=0.009$). With respect to the primary endpoint of definite fatal or non fatal MI, LV mass index ($p=0.026$), T axis ($p < 0.0001$), T amplitude ($p=0.0005$) and heart rate ($p = 0.006$) were all predictive in a multivariate analysis which included treatment, age, smoking history, use of nitrates,diabetes, Rose angina, family history of premature CHD death,widowhood, diastolic BP and cholesterol:HDL ratio. Similar results were found for the extended primary endpoint which included definite or suspect CHD death or non fatal MI. With respect to all cause mortality, minor ST-T changes ($p=0.0045$), SDNN ($p < 0.0001$) and T axis ($p < 0.0001$) were all significantly predictive of outcome in a multi variate analysis. Cardiac vagal tone was highly predictive of outcome ($p < 0.005$) in univariate analyses only.
Conclusion: These results indicate that the electrocardiogram is of significant prognostic value in a population of middle aged men who have not sustained a previous myocardial infarction.

3314 The cardiovascular life course of obese and overweight persons, compared to those with normal weight

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Background Overweight and obesity have been linked to an increased risk of mortality, disability and a number of diseases such as cardiovascular disease, cancer and other metabolic disorders. Their potential impact on life expectancy and lifetime experience of cardiovascular disease has not yet been fully described. Here we compare the total and cardiovascular disease specific life expectancies associated with overweight and obesity at age 40.
Methods We analysed individuals from the Original Framingham Heart study, aged 30-49 and grouped into normal weight, overweight or obese (based on body mass index) at baseline. Mortality and cardiovascular disease incidence rates specific for age and body mass index group were derived by survival analysis within sex and smoking status strata. From these we constructed multistate life tables describing the states free of cardiovascular disease and with cardiovascular disease for each body mass index group and estimated life expectancy and life years lived with cardiovascular disease over the life course. Confidence intervals were derived using a bootstrap procedure.
Results We found surprisingly large decreases in life expectancy associated with overweight and obesity, with forty year old non-smokers losing 3 years due to overweight and 6-7 years due to obesity. Obese smokers lost a striking 13-14 years compared to normal weight non-smokers. Cardiovascular disease caused approximately half of the years of life lost in obese subjects. Although obese people suffer a large decrease in total life expectancy they lived on average 0.6 years more with cardiovascular disease than those with normal weight.
Conclusions Obesity and overweight in adulthood are associated with large decreases in life expectancy, comparable to smoking. As with smoking, the loss of life due to obesity continues to occur decades after exposure. Even taking into account this shortened life expectancy, obese people spend a greater number of years with cardiovascular disease than those with normal weight: obesity both compresses healthy life and increases years lived with disease. The rising world-wide prevalence of obesity highlights the urgent need for more efficient prevention and treatment of overweight and obesity.

3315 Vitamin B6 is a predictor of long-term vascular events in a healthy population in addition to homocysteine and C-reactive protein levels

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Background: Plasma total homocysteine (tHcy) has been recently proposed as a novel marker of cardiovascular risk. Plasma tHcy levels are affected by nutritional intake of vitamin B12, folate, and vitamin B6.
We assessed the predictive value of tHcy, vit. B12, folate and vit. B6 on the long-term occurrence of cardiovascular events in a prospectively recruited population in a nested case-control study with 12-years follow-up, out of the "Martignacco Project", an ongoing epidemiological and primary prevention trial on North-Eastern Italian middle aged men and women initiated in 1987.
Methods: Within 1,051 subjects (509 men and 542 women) recruited in 1987, 69 incident (15 fatal) coronary events (18 myocardial infarctions; 51 newly documented myocardial ischemia) and 40 incident (5 fatal) cerebrovascular events (27 definite strokes; 13 transient ischemic attacks) occurred, until June 1999, in subjects originally free of atherosclerotic cardiovascular disease (cases, n=109). 109 control subjects (subjects remained free of events in the same follow-up period) were matched to cases according to the following variables: age, sex, smoking, hypertension, dyslipidemia, and body-mass-index. On baseline serum samples, obtained from the initial cohort in 1987, tHcy plasma concentration, folate and vitamins B12 and B6, as well as C-reactive protein (CRP) levels, were measured.
Results: We found a significant graded association between tHcy levels and the risk of cardiovascular events (odds ratio, OR, for lowermost vs uppermost quartile = 1.32, 95% CI 1.01-1.73). Serum folate and vitamin B12 did not significantly differ between cases and controls, but were negatively ($P<0.01$) correlated with tHcy. Vitamin B6 did not show correlations with tHcy levels, but differed significantly between cases and controls: For subjects in the uppermost quartile vs the lowermost quartile of vit. B6, OR=0.68 (95% CI 0.49-0.95). For subjects in the lowermost quartile of vitamin B6 and the uppermost quartile of tHcy, the OR was 2.79 (95% CI: 2.06-3.77). Cases and controls were not different as to C-reactive protein levels.
Conclusion: These data confirm the role of tHcy as a long-term independent risk factor for cardiovascular events, but also support the additive importance of a "novel" marker, plasma vitamin B6, independent of tHcy and CRP.

3316 Prognostic risk factors for cardiovascular events, in subjects with familial hypercholesterolemia: 15 years follow-up (1987-2002)

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Background: It is estimated that 200 out of 100,000 individuals suffers from familial hypercholesterolemia, worldwide. However, the influence of several risk factors on all cause mortality, in this subgroup of subjects, has rarely been evaluated. In this work we evaluate the prognostic significance of several risk factors on the outcome of cardiovascular events, in subjects with familial hypercholesterolemia.
Methods: During a 1987-2002, we studied 639 individuals (230 males 49 ± 11 years old and 409 females, 52 ± 9 years old) with defined familial hypercholesterolemia. Baseline measurements of arterial blood pressures, fibrinogen levels, glucose concentration, total cholesterol levels, high and low density lipoprotein cholesterol, Apo A-I & B, Lp(a), and triglycerides were evaluate for their prognostic significance, with respect to age, sex and the prevalence of the common cardiovascular risk factors (body mass index, smoking, hypertension, diabetes mellitus) as, potential, confounders. All laboratory measurements were quality controlled and a detailed database was developed. Cox proportional hazards models were applied in order to evaluate the investigated associations.
Results: During the follow up period 87 cardiovascular events were observed in familial hypercholesterolemic patients. Fifty-three (61%) of the events were observed in males and the rest of them in females (39%). The application of the log-rank test raised the superiority of women compared to men in the events free survival ($p = 0.005$). The age adjusted 15-year event rate was 3% (87 events/2915 person-years). The multivariate analysis showed that smoking (hazard ratio=2.28, $p = 0.023$), LDL/HDL ratio (HR=1.23, $p = 0.041$) and presence of hypertension (HR=3.18, $p = 0.036$), were independently associated with 15-year cardiovascular events in the investigated sample. The applied sensitivity – specificity analysis showed that LDL values 8-times than HDL constitute a cut-off point that predicts with accuracy an adverse cardiovascular outcome. No associations were found between the outcome and the other investigated factors in the long-term assessment of our patients.
Conclusions: With the power of the 15 years of prospective evaluation our analysis showed that increased smoking habits, presence of hypertension and LDL levels 8-times more than HDL predicts an adverse cardiovascular event, in patients with familial hypercholesterolemia. No associations were found between the outcome and the other investigated clinical and biochemical factors.

3317 Triglycerides as predictor of late mortality in healthy hyperlipidemic men

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Objective: The aim was to study cholesterol, triglycerides (TG), smoking and blood pressure as potential predictors of 24 years mortality in hyperlipidemic middle aged men.
Background: We studied 104 healthy men aged 40-49 years with start values of total serum cholesterol > 7.75 mmol/l and fasting triglycerides >2.95 mmol/l within the randomised diet and smoking cessation trial of the Oslo study (n=1232).
Results: 33 subjects died during the 24 years observation period.
Only triglycerides and smoking were significantly related to mortality.
Analysis for trend through quartiles of triglycerides (table I) showed statistical significance (p= 0.049).
Subjects in the lowest TG quartile (2.95-3.18 mmol/l) had 70% reduction in mortality compared to the remaining subjects (>3.18 mmol/l) (RR= 0.30, 95% CI 0.10-0.90, p= 0.014). Non-smokers had 60% reduced mortality compared to smokers (RR=0.40, 95%CI 0.17-0.94, p=0.019).
When TG and mortality were studied in a Cox regression analysis, with age and smoking as independent variables, TG was significantly related to mortality, 1.quartile vs 2.,3. and 4th quartile: RR=0.24, (95% CI 0.07-0.77), p=0.02. For smoking the Cox analysis showed a RR=0.39 (95%CI 0.15-1.02) p= 0.054.

Triglycerides	1.quartile	2.quartile	3.quartile	4.quartile
mmol/l	2.95 - 3.18	3.18 - 3.8	3.8 - 4.5	4.5 - 13.6
Dead (n)	3	9	12	9
Mortality % p=0.049	11.5	34.5	46.2	34.6

Triglycerides (mmol/l), quartiles vs Mortality

Conclusion: This study indicates that high levels of fasting triglycerides (>3.2 mmol) are associated with 3-fold increased late mortality in healthy men with combined hyperlipidemia.

3318 Conventional risk factors underestimate subclinical coronary artery disease in younger asymptomatic subjects

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Background: The incremental value of coronary artery calcification (CAC) as compared to conventional risk factors in identifying subjects with subclinical coronary artery disease (CAD) has been unclear. We defined subclinical CAD as the presence of CAC, detected by multi-row detector spiral computed tomography (MDCT), and sought to compare its presence with the conventional coronary risk factors in relation to age.
Methods: We studied 445 participants (mean age 55±7 years old, 89% male) in the annual check-up program at our institute. Subjects over 40 years without known CAD were included. All underwent routine physical examination, ECG stress test, blood analysis and MDCT with prospective ECG triggering. Subjects were divided into a younger age group below 50 years (n=123, mean age 46±4) and an older one over age 50 (n=322, mean age 58±6).
Results: The prevalence of CAC was 27% in the youngers and 60% in the older group (p<0.01). Median (Q1,Q3) of total calcium score were 22 (13,73) and 54 (13,128) respectively (p<0.01). Prevalence of risk factors are given in the table.

Age group:	40-50 years	51-75 years
Hypertension	16%	31% **
Smoking	11%	18%
Diabetes Mellitus	3%	9% *
Hypertrigliceridemia	27%	20%
LDL>160mg%	10%	10%
HDL<40mg%	55%	38% *

*p<0.05, **p<0.01

Logistic regression analysis for the prediction of CAC presence was not significant in the younger group for all the risk factors while in the older subjects hypertension, smoking and hyperlipidemia (all types) were significant independent predictors of CAC with O.R. (95% C.I.) of 2.53 (1.35 - 4.1,p=0.025), 1.42 (1.1-1.8, p=0.025) and 1.26 (1.1-1.9, p=0.049) respectively.
Conclusions: In this cohort, conventional risk factors failed to predict the presence of subclinical CAD in asymptomatic subjects younger than 50 years, supporting the potential of CAC detection as a screening tool for this age group.

BENEFITS OF CARDIAC REHABILITATION

3319 Reduction of absolute coronary risk following a combined lifestyle intervention programme in patients with coronary heart disease

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Objective: In order to evaluate the prognostic impact of a multidisciplinary lifestyle intervention programme (IP) we included 162 males with documented coronary heart disease (CHD) for a 2-year follow-up study. They were randomised into two groups: 1. IP group (n=79) with regular physical exercise (physiotherapist), dietary advice (dietician) and general lifestyle measures including smoking cessation (study nurse). A research physician was responsible for their medical treatment in accordance with recent guidelines for secondary prophylaxis. 2. Usual care group (UC, n=83), which included regular follow-up in our outpatient clinic or by their general practitioner.
Method: The absolute CHD risk at baseline and during follow-up was based upon the Cox proportional hazards model applied in the estimation of 5-year risk of fatal CHD and non-fatal myocardial infarction in the placebo group of WOSCOPS. All our patients were categorised as having angina pectoris according to the Rose questionnaire. The following cluster of risk factors were put into the model: Age, blood pressure, history of hypertension, family history of CHD, total cholesterol/HDL ratio, smoking status, minor ST-T changes in the ECG and fasting blood glucose.
Results: 5-year risk of fatal CHD and non-fatal myocardial infarction(% ± 1SD)at baseline: IP-group=15.3±9.0, UC-group=14.0±8.6, at 6 months: IP=11.7±9.0, UC=12.9±10.2, at 2 years: IP=12.2±11.9, UC=13.7±11.8. p=0.008 for difference in change from baseline to 6 months, p=0.023 for difference in change from baseline to 2 years. The use of statins, betablockers, aspirin and ACE-inhibitors was identical in both groups. During the study there were 35 cardiovascular hospitalisations in the IP group and 52 in the UC group.
Conclusions: The CHD risk was reduced by approximately 20% in the IP group versus no change in the UC group in spite of the fact that both groups had comprehensive and identical medical prophylaxis.

Group	Baseline	6 months*	2 years**
IP (n=79)	15.3 + 9.0	11.7 + 9.0	12.2 + 11.9
UC (n=83)	14.0 + 8.6	12.9 + 10.2	13.7 + 11.8

3320 Two-year benefit of cardiac rehabilitation program on quality of life and cost-effectiveness in patients with coronary artery disease

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Background: With the changing paradigm of managing patients with coronary artery disease (CAD) in the last decade and the relatively few randomized, controlled studies, it is uncertain if a cardiac rehabilitation program (CRP) could be cost-effective and lead to improvement of quality of life (QOL). This study evaluated the effect of CRP on QOL and its cost-effectiveness upon completion of the program at 2-year.
Methods: A prospective, randomized, controlled study was performed in 269 patients (mean age of 64±11 years, 76% male) with recent acute myocardial infarction (AMI, n=193) or after elective percutaneous transluminal intervention (PCI, n=76). They received either an 8-week CRP (n=181) or conventional therapy (control group, n=88) at a ratio of 2 to 1. QOL assessment (SF-36 and Symptoms Questionnaire) was performed in all the 4 phases. Direct healthcare cost was calculated while cost-utility of CRP was estimated as money spent (in US$) per quality adjusted life-year (QALY) gained. The prescription rates of statin and angiotensin converting enzyme inhibitor (ACEI) were 62% and 64% respectively. In the CRP group, 6 out of 8 SF-36 dimensions were significantly improved by phase 2, i.e. physical functioning (<0.001), physical role (<0.001), vitality (<0.001), social functioning (<0.001), emotional role (<0.001) and mental health (0.003); and were maintained at phase 4. Patients were less anxious and depressed, and were more relaxed and contented. In the control group, none of the SF-36 dimension was improved by phase 2, and was only 4 in phase 4 (physical functioning [p=0.002], physical role [p<0.001], vitality [p=0.04] and emotional role [p=0.01]) while bodily pain was increased. Symptoms were unchanged except increased hostility score. There was a significant gain in net time trade-off in the CRP group at phase 2 (CRP:0.031±0.028, controls: -0.049±0.031, p<0.005). The direct health care expenses in the CRP and control groups were $15,292 and $15,707/patient respectively. Therefore the cost-utility calculated was $640 saved/QALY gained in the CRP group. Saving attributable to CRP was primarily explained by the lower rate (13% Vs 26% of patients, X^2=3.9, p<0.05) and cost of subsequent PTCA (p=0.01).
Conclusions: In the contemporary era of managing patients with CAD where a high rate of statin and ACEI was used, a short-course CRP was highly cost-effective in the provision of better QOL in patients with recent AMI or PCI. In addition, the improvement of QOL is faster and sustained for at least 2 years after CRP.

3321 Activation of vagal reflexes, exercise training and long-term survival after a myocardial infarction

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We have previously shown that exercise-induced increase in Baroreflex Sensitivity (BRS) improves survival at the experimental level; such evidence is still lacking in patients after myocardial infarction (MI). We studied 95 consecutive male patients (pts) surviving a first uncomplicated MI who were randomly assigned to a 4-week endurance training period (T) or to no training (NT). Age (51±8 vs 52±8 years), site of MI (anterior 41% vs 43%), left ventricular ejection fraction (52±13 vs 51±14%), and BRS (7.9±5.4 vs 7.9±3.4 ms/mmHg) did not differ between the two groups. After 4 weeks training, BRS - as a marker of vagal reflexes - increased by 26% (from 7.9±5.4 to 9.9±6.4 ms/mmHg, p=0.04) in T, while it did not change in NT patients. During a 10-year follow-up, cardiac mortality was 12% in T and 26% in NT (p=0.07), while revascularization procedures were performed in 13% and 18% (NS) and beta-blockers were used in 16% and 13% (NS) in T and NT pts respectively. When T pts were grouped according to an exercise-induced increase in BRS > 3 ms/mmHg, cardiac mortality was strikingly lower compared to that of the T patients without such a BRS increase plus the NT patients (0/16 vs 18/79, p=0.04). Age, ejection fraction, anterior MI, myocardial revascularization and beta-blockade did not differ also between these two groups.
Conclusion: Post-MI exercise training can favourably modify long-term survival, provided that is associated to a clear shift of the autonomic balance toward an increase in vagal activity.

3322 The effect of exercise training on baroreflex control of heart rate and sympathetic activity in patients after acute myocardial infarction

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Autonomic imbalance has been found in patients after acute myocardial infarction (AMI) and have been associated with an increased risk of cardiac mortality. Although exercise training (ET) is associated with reduction in sympathetic tone, it is unknown whether ET improves sympathetic nerve traffic in patients after AMI. The aim of this study was to examine the effects of ET on baroreflex control of heart rate and muscle sympathetic nerve activity (MSNA) in patients after AMI.

Methods: Twenty patients with an uncomplicated AMI were prospectively randomized to training group (60% of peak heart rate, 40min/day, 4days/week, n=10, LVEF52±6%) or to control group (n=10, LVEF50±9%). Arterial blood pressure, heart rate and MSNA (microneurography at a peroneal nerve) were measured at baseline and after 4 weeks. Measurements were performed at baseline, and during baroreceptor stimulation (phenylephrine infusion) and baroreceptor deactivation (nitroprusside infusion).

Results: There were no significant differences in baseline data between the 2 groups. Peak oxygen consumption increased 9.0±6.6% with ET. Resting MSNA reduced from 31±13 to 24±8 bursts/min in training group but not in control group. Arterial baroreflex sensitivity did not change in both groups after 4 weeks. MSNA response to baroreceptor stimulation increased significantly in training group (%change of integrated activity from -43±23 to -70±23) but not in control group. In contrast, MSNA response to baroreceptor deactivation was similar in the 2 groups.

Conclusion: Exercise training lowers sympathetic nerve traffic in patients after AMI. This is accompanied by a restoration of baroreflex restraint on sympathetic nerve drive.

3323 Is coaching a substitute for cardiac rehabilitation in the management of cardiac risk factors?

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Background: We have shown that personalised coaching over the telephone (The Coach Program) is highly effective in improving risk factor (RF) status in patients with coronary heart disease (CHD). The COACH study has allowed us to contrast the effectiveness of coaching (TCP) with cardiac rehabilitation (CR) in its impact on RF.

Methods: Retrospective analysis of a multicentre RCT performed by cardiac units of six teaching hospitals in Melbourne, Australia. 679 (86%) of 792 patients with CHD completed a randomised trial of TCP vs usual care (UC) to improve RF status. CR was performed by 176 (53%) of 331 TCP patients and by 199 (57%) of 348 UC patients. Outcome measures included: changes in total cholesterol (TC), plasma triglyceride (TG), HDL-C and LDL-C, body weight (BW), fasting glucose (FBG), blood pressure (BP), cardiac depression score (CDS), Spielberger State (STAI) for anxiety, from baseline (in-hospital) to 6 months post-randomisation. In addition, 6 month post-randomisation levels of smoking, physcial activity, symptomatic status and general well-being were measured. Four groups were thus created: TCP/CR, TCP/No CR, UC/CR, and UC/No CR. The variables were compared by appropriate parametric and non-parametric statistics.

Results: Both TCP and CR produced a highly significant effects on the change in TC and LDL-C ($P<0.0001$). Neither intervention resulted in change of TG or HDL-C. Both TCP and CR resulted in large impacts on BW ($P<0.0001$). TCP/CR had a greater impact on regular walking patterns than either CR of TCP alone and all were superior to UC ($P<0.0001$). TCP/CR was more effective than either CR or TCP alone in reducing anxiety levels and all were superior to UC ($P=0.0045$). Both TCP and CR were effective in reducing the prevalence of chest pain and breathlessness and dyspnoea and in improving general health at 6 months post-randomisation ($P<0.0001$).

Conclusion: Retrospectively both TCP and CR were highly effective improving RF status. TCP is an alternative approach for the large proportion of patients not able or willing to attend CR.

3324 Evaluation of the immunoregulatory role of physical training in chronic heart failure: a randomized crossover study

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Objectives: To investigate the effects of physical training on peripheral immune responses expressed by circulating proinflammatory cytokines and soluble apoptosis mediators Fas (sFas) and Fas Ligand (sFasL), in chronic heart failure (CHF) patients and healthy controls.

Background: Recent investigations have shown an overexpression of circulating proinflammatory cytokines and soluble apoptosis mediators in patients with CHF, which may be related to their exercise intolerance and clinical deterioration.

Methods: Plasma levels of tumor necrosis factor-a (TNF-a), soluble TNF receptors I and II (sTNF-RI and sTNF-RII), interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), sFas and sFasL were measured in 24 patients with stable CHF (New York Heart Association class II-III; left ventricular ejection fraction: 23.2±1.3%) and in 20 normal control subjects before and after a 12-week program of physical training in a randomized crossover design. Functional status of CHF patients and healthy controls was evaluated by using cardiorespiratory exercise test to measure peak oxygen consumption (VO2max).

Results: In CHF patients, physical training produced a significant reduction in plasma levels of TNF-a (7.5±1.0 vs 4.6±0.7 pg/ml, $p<0.001$), sTNF-RI (3.3±0.2 vs 2.7±0.2 ng/ml, $p<0.05$), sTNF-RII (2.6±0.2 vs 2.3±0.2 ng/ml, $p=0.06$), IL-6 (8.3±1.2 vs 5.9±0.8 pg/ml, $p<0.005$), sIL-6R (34.0±3.0 vs 29.2±3.0 ng/ml, $p<0.01$), sFas (5.5±0.7 vs 4.5±0.8 ng/ml, $p=0.05$) and sFasL (34.9±5.0 vs 25.2±4.0 pg/ml, $p<0.05$), as well as a significant increase in VO2max (16.3±0.7 vs 18.7±0.8 ml/kg/min, $p<0.001$).

Good correlations were also found between training-induced increase in VO2max and training-induced reduction in levels of proinflammatory cytokine TNF-a ($r=-0.54$. $p<0.01$) and apoptosis inducer sFasL ($r=-0.57$, $p<0.005$) in CHF patients. On the contrary, no significant difference in circulating cytokines and apoptotic markers was found with physical training in normal subjects.

Conclusions: Physical training modulates beneficially circulating proinflammatory cytokines and sFas/sFasL system in patients with CHF. These immunomodulatory effects may be related to the training-induced improvement in functional status of CHF patients.

GROWTH FACTOR REGULATION OF CARDIAC SIZE

3333 Variation at the beta-1 adrenoceptor gene locus affects left ventricular mass

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Aims: Left ventricular (LV) mass is an important cardiovascular risk factor. Beta-1 adrenoceptors (B1AR) are predominately located in the heart and their variation may, therefore, affect LV mass. A known polymorphism of the B1AR changes the amino acid at position 389 from glycine to arginine within an area critical for G-protein coupling and so cell signalling. The arginine-form of the receptor has been demonstrated to have increased GTP binding and cAMP generation. We therefore examined the relationship between this variation in the B1AR gene and the effect on LV mass in two contrasting populations.

Methods and Results: The first population studied consisted of 249 patients attending a renal clinic, 37% of whom were on renal replacement therapy (RRT). LV mass index (LVMI) was calculated by echocardiography. Individuals were categorised CC if both alleles encoded for arginine at position 389 and GG if both alleles encoded glycine. The GG group had a significantly higher LV mass index when compared to the other 2 groups, CG:GG $p= 0.02$ and CC:GG $p=0.01$ (see table). This relationship strengthened further when patients on RRT were omitted (CC:GG $p <0.001$).

	Number	% of 249	Mean LVMI
CC	127	51	130.1
CG	103	41	132.5
GG	19	8	160.8

Frequency of different B1AR genotypes and LVMI

In a second study, the effect of B1AR genotype on electrocardiographically measured LV mass was studied. 2280 subjects were genotyped for the B1AR polymorphism. No significant difference was found between LVMI and genotype after correction for age, BP and height and analysing separately for sex.

Conclusion: Genetic variation of the beta-1 adrenoceptor may well be important in defining LV mass in pathological circumstances.

3334 A specific type 4 cAMP phosphodiesterase isoform regulates beta-adrenoceptor signalling in neonatal rat cardiac myocytes

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The large multigenic superfamily of phosphodiesterases (PDEs) provides the sole means of degrading the ubiquitous second messenger cyclic AMP (cAMP) within cells. Over 30 cAMP hydrolysing PDE isoforms are known and it is thought that this multiplicity allows discrete intracellular pools of cAMP to be maintained, thus enabling differential activation of the many targets of cAMP signalling.

We closely defined the PDE activities present in a neonatal rat cardiac myocyte culture model with particular focus on type 4 PDE (PDE4) where the precise isoforms present were defined by Western blotting and RT-PCR. We then investigated PDE control of beta-adrenoceptor (B-AR) mediated cAMP signalling in these cells. Stimulation with 10μM isoproterenol in the presence of PDE4 inhibitor (but not PDE3 or PDE2 inhibitor), caused a 5.5-fold increase in cAMP concentration compared to agonist alone ($p<0.001$), indicating that PDE4 activity was responsible for controlling B-AR mediated cAMP generation. Selective immunoprecipitation of PDE4 subclasses showed that PDE4D activity increased upon isoproterenol stimulation (16±0.7 to 25±2 pmol/min/mg at 20 minutes, $p=0.0011$), suggesting a particular role for this subclass. Immunoprecipation of the beta2-adrenoceptor co-precipitated PDE4 activity and Western blotting confirmed that this activity was due to PDE4D isoforms. Attenuation of specific PDE4D isoforms was achieved by adenoviral overexpression of catalytically inactive mutants and this potentiated the phosphorylation of B-AR linked cAMP targets without affecting other PKA controlled processes.

In summary, we have shown that in rat cardiac myocytes, beta-adrenoceptor cAMP signalling processes appear to be selectively controlled by a specific receptor bound PDE4 isoform. This has clinical implications as assignment of cellular targets to specific PDE isoforms may ultimately allow the design of highly selective pharmacological agents. An example in cardiac myocytes might be the development of inotropic agents without membrane destabilising arrhythmogenic effects.

3335 The role of PKCz and cPLA2 in the negative regulation of IGF-1 signaling and cardiac growth

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Cytosolic phospholipase A2 (cPLA2) releases arachidonic acid (AA) from phospholipids. Since AA is converted to eicosanoids, cPLA2 plays a critical role in many cellular processes. We report 3 novel functions of cPLA2-regulation of normal, stress-induced hypertrophic growth of the heart, and of IGF-1 signaling. Studies in cPLA2-deficient mice (-/-) demonstrated differential organ growth and increased heart/body wt.ratio in (-/-) mice. Both groups had identical myocardial function and physiology. The (-/-) mice had significantly thicker ventricles from increased cardiomyocyte size. Pressure-overload (PO) caused exaggerated hypertrophy in (-/-) mice. Both Akt and ERK1/2 were constitutively activated in the unstressed hearts of (-/-) mice. PO lead to significantly greater activation of PI3-K, Akt, GSK-3b, p70S6 kinase and ERK1/2 in the hearts of (-/-) mice. It has been shown that IGF-1 plays a pivotal role in mammalian postnatal cardiac growth. Studies in cells derived from mice with a cPLA2 deletion demonstrated that exogenous IGF-1 activated these intracellular mediators in a similar pattern to the PO exposed (-/-) group. IGF-1 administered in vivo lead to a similar profile of activation in (-/-) hearts. The "hyper-responsiveness" of IGF-1 signaling in (-/-) mice was not due to increases in endogenous IGF-1 production. Additionally, PDGF caused more enhanced activation of these signaling mediators in (+/+) and not in (-/-) cells, excluded a generalized growth factor response. The enhanced responsiveness of IGF-1 signaling was specific to cPLA2, and was confirmed by pharmacological inhibition of cPLA2 using inhibitors; AACOCF3 and MAFP in (+/+) cells, or conversely, rescuing the phenotype by gene transfer with adenovirus encoding cPLA2 in (-/-) cells. We found that cPLA2 negatively regulated IGF-1-dependent signaling via effects at the level of the IGF-1 receptor and IRS-1. The enhanced binding of IRS-1 to the IGF-1R was due to a failure to recruit PKCz, a recently described negative regulator of IRS-1. PKCz was not activated by PDK1 at Thr410 in vitro or in vivo in (-/-) mice. However, in the presence of arachidonic acid, PDK1 was able to phosphorylate (Thr410) and fully activate PKCz, "rescuing" the (-/-) phenotype. The disruption of this negative input in the cPLA2-deficient mouse leads to enhanced activation of the growth-regulatory PI3-K and ERK1/2 pathways, resulting in exaggerated normal and pathologic growth of the heart. These studies add the regulation of growth of the heart and modulation of IGF-1 signaling to the list of processes regulated by cPLA2.

3336 Calcineurin and protein kinase C are involved in insulin-like growth factor-1-induced hypertrophy of cultured adult rat ventricular myocytes

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It has been recently reported that insulin-like growth factor-1 (IGF-1) increases intracellular calcium levels in cardiomyocytes. Thus, we examined the roles of calcineurin and protein kinase C in IGF-1-induced hypertrophy in adult rat ventricular myocytes. Primary cultures of adult rat ventricular myocytes were prepared from the ventricles of 14-16 week-old male Sprague-Dawley rats. First, we studied effects of IGF-1 on the morphology of adult rat ventricular myocytes. Myocyte surface area was significantly increased by IGF-1 (2268 ± 571 to 3018 ± 836 μm^2, $P < 0.01$). This hypertrophic effect of IGF-1 was blocked by genistein (tyrosine kinase inhibitor) and PD98059 (MEK inhibitor). These data suggest that IGF-1 produces adult rat ventricular myocyte hypertrophy by a tyrosine kinase-MEK mediated pathway as reported in neonatal cardiomyocytes. IGF-1-mediated adult rat ventricular myocyte hypertrophy was also attenuated by cyclosporine A (calcineurin inhibitor), staurosporine and chelerythrine (protein kinase C inhibitors). IGF-1 markedly increased calcineurin activity (8.7 ± 1.2 to 98.0 ± 54.3 pmol/hr/mg, $P < 0.01$), and this activation was completely blocked by the pre-treatment with cyclosporine A (8.5 ± 11.4 pmol/hr/mg, $P < 0.01$) and chelerythrine (2.3 ± 2.7 pmol/hr/mg, $P < 0.01$). These data suggest that IGF-1 activates calcineurin by a protein kinase C-dependent pathway. Increased mRNA expression of atrial natriuretic factor by IGF-1 was inhibited by cyclosporine A ($P<0.01$). Our data indicate that IGF-1 induces adult rat ventricular myocyte hypertrophy by protein kinase C and calcineurin-related mechanisms. IGF-1 activates calcineurin through protein kinase C. The fact that elevated calcineurin activity and induced atrial natriuretic factor mRNA expression by IGF-1 were blocked by cyclosporine A further supports the notion that calcineurin is critically involved in IGF-1-induced adult rat ventricular myocyte hypertrophy.

3337 Myocardial regulation of IGF binding proteins in two models of hypertension

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Background: GH treatment has been shown to increase cardiac mass, a response that is most likely mediated by insulin-like growth factor-I (IGF-I). In several rat models such treatment was associated with improved cardiac function, supporting a beneficial role for IGF-I. The biological activity of IGF-I is modulated by several highly specific IGF binding proteins (IGFBPs). Very little is known about the cardiac expression and regulation of these proteins in response to pressure overload.

Methods: We measured cardiac mRNA levels of the IGFBPs in two different models of hypertension, namely in rats infused with angiotensin II (ang II) through osmotic minipumps, and in salt-fed Dahl salt-sensitive (S) rats. The different mRNAs were detected by Northern blotting using radiolabeled specific probes. All signals were normalized for GAPDH.

Results: As expected, in both models increased blood pressure was associated with increased cardiac mass and increased tissue levels of the growth factor IGF-I. Ang II infusion (500 ng/kg/day) decreased cardiac IGFBP-3 mRNA by 54±9% and 41±5% at day 3 and 7, respectively ($P<0.05$). In this model the inhibitory IGFBP-4 was increased by 79±19% ($P<0.05$) at day 3, but returned to levels of control animals after 7 days. IGFBP-5 mRNA was not changed. After 4 weeks of high salt diet, hypertensive Dahl S rats had significantly higher IGFBP-4 levels (63% increase) compared with normotensive Dahl salt-resistant (R) rats ($P<0.05$). In this model no changes were observed for IGFBP-3 or IGFBP-5.

Conclusions: The increase in IGFBP-4 in both models suggests that this protein is important in regulating IGF-I activity in cardiac tissue under conditions of pressure overload. In addition, the combination of high cardiac IGF-I and low IGFBP-3 in ang II-infused rats likely facilitates development of cardiac hypertrophy in response to ang II, since IGFBP-3 is generally thought to inhibit IGF-I activity. This decrease in IGFBP-3 was not observed in hypertensive Dahl rats, and is therefore probably due to a blood-pressure independent mechanism.

3338 Different growth factor activation between right and left ventricle in experimental volume overload

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Cardiac overexpression of angiotensinogen (AGT) and insulin-like growth factor (IGF)-I genes has been reported in experimental volume overload. Different hemodynamic response to volume overload in left and right ventricles might influence the local expression of cardiac growth factors. Therefore we investigated AGT, IGF-I, and prepro endothelin (ppET)-1 mRNAs in right and left ventricles of 15 adult pigs (30+5 kg) after the creation of aorta-cava fistula distal to the renal arteries causing a 50% increase in cardiac output. Six animals were sham-operated.

At baseline, 2 weeks, 1, 2 and 3 months after surgery hemodynamic and echocardiographic measurements were recorded. Animals were then euthanized and myocardial specimens were taken for RT-PCR studies.

In the left ventricle volume overload did not cause significant changes in ventricular pressure and contractility (Vcf). RT-PCR revealed a selective overexpression of IGF-I mRNA at 2 weeks (2-fold) which remained elevated at following times in a close association to the increase in left ventricular mass (from 59±9 to 92±7 and 254±23 g at 2 weeks and 3 months respectively, $p<0.05$ for both). Conversely, in the right ventricle both systolic and end-diastolic pressure significantly increased at 2 weeks ($p<0.05$ vs baseline for both) and remained elevated vs baseline throughout the study. RT-PCR analysis showed overexpression of AGT and IGF-I mRNAs at 2 weeks ($p<0.05$ for both) and ppET-1 transcript at 1 month (24-fold). All genes remained overexpressed at the following experimental times ($p<0.05$).

In conclusion: a differential pattern of growth factor response to volume overload is detectable in left and right ventricle: 1) AGT and ppET-1 mRNA expression are restricted to right ventricular myocardium which had to face both pressure and volume overload, 2) IGF-I gene is overexpressed in both ventricles independently on AGT gene activation 3) in left ventricle IGF-I expression is associated with marked hypertrophy without impairment of myocardial contractility.

NOVEL MECHANISMS IN THE CONTROL OF CARDIAC FUNCTION

3339 Acute mechanical stretch of rabbit myocardium regulates expression of SERCA2a via the calcineurin pathway

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Introduction: The regulation of gene expression of calcium cycling proteins in the myocardium is poorly understood so far. In this study we investigated the effect of a 6-h-stretch period on the expression of SERCA2a and NCX in non-failing rabbit myocardium. Both are key proteins for the regulation of cytosolic Ca^{2+}-concentration and show different patterns of expression in cardiac hypertrophy and failing myocardium. There is evidence for a wall tension-dependent regulation of SERCA2a in the published literature.

Methods: Right ventricular trabeculae from non-failing rabbit myocardium were dissected and mounted in a culture chamber in tissue culture medium (1.75 mM Ca^{2+}) at 37°C and electrically stimulated at 1 Hz. The trabeculae were stretched to obtain a resting tension of 95% Lmax and kept stretched for 6 h in culture.

Control preparations remained at slack for 6 h. SERCA2a and NCX1 mRNA levels were measured by competitive NASBA reaction. Protein levels were measured by Westernblot analysis. Calsequestrin served as the house-keeping gene.

Results: We observed a significantly higher expression of SERCA2a mRNA in stretched trabeculae compared to slack preparations (stretch (n=9) 1.08xe8 ± 6.0xe7 vs. slack (n=9) 4.23xe7 ± 2.5xe7, $p < 0.02$). RNA data were confirmed by western blotting with regard to protein expression of SERCA2a, which showed a significantly higher expression on protein level as well (stretch 0.85 ± 0.06 vs. slack 0.49 ± 0.15, $p < 0.01$). After addition of Cyclosprin A (CsA) for inhibition of calcineurin activity we observed a significant decrease of the stretch-induced SERCA2a upregulation (stretch without CsA (n=9) 1.08xe8 ± 6.0xe7 vs. stretch with CsA (n=9) 4.21xe7 ± 2.5xe7, $p < 0.02$). For NCX1 neither RNA nor protein data showed significant differences.

Conclusion: Our data show, that the expression of SERCA2a depends on the wall tension (load). Acute stretching of rabbit myocardium leads to an upregulation of SERCA2a expression, which may be useful in controlling stretch-induced increase of cytosolic Ca^{2+}. This regulation appears to be mediated via an activation of calcineurin activity by acute stretch. So acute inrease of wall tension leads, in contrast to the decreased expression of SERCA2a in chronic failing myocardium or chronic hypertrophy, to an upregulation of SERCA2a.

3340 Heme oxygenase modulates response of cardiac muscle to beta adrenergic stimulation

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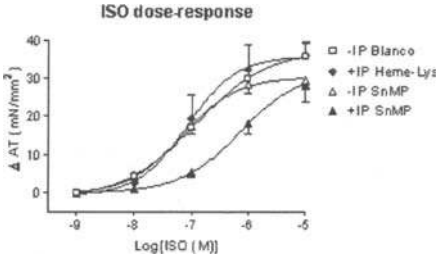
Introduction: Heme oxygenase (HO) catalyzes the first and rate limiting step in heme metabolism, producing equimolar quantities of carbon monoxide (CO), biliverdin and free iron. HO-1 (also known as 'Heat shock protein' 32) is the inducible isoform (induced by heme, heavy metals, heat shock, cytokines and endotoxin), which plays a major role in the defence against oxidative and cellular stresses.

Methods: HO-1 was induced by intraperitoneal injection (IP) of 75μg/kg hemin in New Zealand White rabbits 24 and 48 hours before measuring isometric contractions of right ventricular papillary muscles. Muscles were randomly assigned to a group (n=7) with heme-lysinate (HO substrate, 10μM) and a group (n=8) with stanneous-mesoporphyrin (SnMP, HO inhibitor, 30μM). A dose-response to isoproterenol (ISO, 10^{-9} to 10^{-5} M) was done in both groups, and all experiments were done with L-NMMA to block NO-synthase activity. The same dose-response was repeated in two groups of muscles (with or without SnMP) of control rabbits without previous induction of HO-1.

Results: Maximal inotropic response to ISO was not significantly affected by HO-1 induction or HO-1 inhibition. However, log(EC50) of ISO dose-response for active tension (AT) shifted from -6.9 ± 0.2 in muscles with induced HO-1 to -6.0 ± 0.2 in muscles with induced but inhibited HO-1. On the other hand, log(EC50) was not affected by inhibition without induction or induction without inhibition.



ISO dose-response.

Conclusion: Our results indicate that inhibition of HO decreases sensitivity of cardiac muscle contraction to beta adrenergic stimulation. However, the effect of inhibition appears only after induction of HO-1. This effect might be explained by a decrease in cGMP content by inhibition of CO production.

3341 The positive inotropic effect of endothelin-1 depends on Na^+/H^+ exchange in failing human myocardium

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Introduction: Endothelin-1 (ET-1) exerts direct positive inotropic effects in the human heart. However, it is controversial whether these inotropic effects are Ca^{2+}-dependent or result from intracellular alkalinization with enhanced Ca^{2+}-responsiveness of the myofilaments secondary to activation of the Na^+/H^+ exchanger (NHE-1). We tested the effects of NHE-1 inhibition on intracellular pH-changes and developed force after ET-1 in isolated failing human myocardium.

Methods: Isolated left ventricular trabeculae (n=25) were electrically stimulated (basal stimulation rate 1 Hz, 370C, isometric contractions). The muscles were loaded with the fluorescent pH-indicator BCECF-AM (15μM for 45 min). ET-1 (0.1 μM) was added under steady-state conditions in either bicarbonate-containing (Tyrode) or bicarbonate-free (HEPES) buffer. In a subgroup of experiments HOE-642 (3 μM) was added 20 min before the application of ET-1. PH and force-parameters were recorded for 60 min. PH-signals after each experiment were calibrated with the "high-K^+-Nigericin"-method. Average values are given as means ± SEM, analysed by the unpaired students t-test. Values of $p<0.05$ were considered significant.

Results: In bicarbonate-free HEPES buffer, HOE-642 resulted in a decline in force (by -57.3±2.7%, $p<0.05$) and an increase in pHi from 7.20±0.04 to 7.33±0.04 ($p<0.05$). ET-1 increased force by 23.1±7.9% ($p<0.05$) associated with a slight decline in pHi. HOE-642 prevented the effect of ET-1 on force and pHi in HEPES buffer. In bicarbonate-containing buffer the inotropic response to ET-1 was larger (42.6±2.3%, $p<0.05$) without significant changes in pHi. HOE-642 only partially prevented the inotropic response to ET-1 in Tyrode's solution (22.8±5.7%, $p<0.05$).

Conclusion: NHE-1 is activated under basal experimental conditions in failing hearts and contributes to force generation possibly by induction of reverse-mode Na^+/Ca^{2+} exchange. ET-1 exerts positive inotropic effects which are related to NHE-1 activation but are largely independent from changes in pHi.

3342 Spontaneous calcium release from SR is caused by increased intracellular sodium due to increased activity of Na/H-exchanger in failing myocytes

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Background: Spontaneous release of calcium from SR is increased in failing myocytes causing a higher incidence of calcium after-transient, which underlies delayed after potentials (DAD'S) and arrhythmias. We hypothesize that increased sodium ($[Na^+]_i$), secondary to up-regulated Na^+/H^+-exchange (NHE) activity, underlies the increased incidence of calcium after-transients and DAD's.
Methods: Heart failure is induced by combined volume and pressure overload in rabbits. $[Ca^+]_i$ and $[Na^+]_i$, were measured with the fluorescent probes indo-1 and SBFI in myocytes from control (n=5) and in failing rabbit hearts (n=12). DAD's were measured with the voltage sensitive fluorescent probe annepp. Calcium after-transient and DAD's were elicited after cessation of rapid pacing (3Hz) in the presence of 100 nM noradrenaline.
Results: $[Na^+]_i$ and $[Ca^+]_i$ were higher in failing myocytes 9.8±0.4 mM and 184 ±13.3 nM compared to control 6.2±0.3 mM and 84±8.9. Inhibition of NHE-activity with cariporide, a specific inhibitor resulted in a decrease of both $[Na^+]_i$ and $[Ca^+]_i$ in failing myocytes to almost control values without effect in control myocytes. In none of the myocytes (n=15) of control rabbits, but in most of the myocytes (32 out of 36) of failing rabbits calcium after-transients and DAD's could be evoked. The incidence of calcium after-transient and DAD's as well as their amplitudes were positive related to the $[Ca^+]_i$ just before the onset of the calcium after-transients. After inhibition of NHE with cariporide the incidence of calcium after-transient and DAD's in these myocytes was significantly reduced (4 out of 36). The four myocytes with after-transient and DAD's had significantly reduced amplitudes. Washout of cariporide increased the incidence to previous values (30 out of 36) an increased their amplitudes.
Conclusion: Disturbed sodium handling in failing myocytes causes an increase of cytosolic calcium resulting in an increase of the incidence of calcium after-transient and DAD's.

3343 Transgenic overexpression of the cardiac EF-hand Ca^{2+} binding protein S100A1: a novel strategy to increase myocardial contractile performance

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Background: Heart failure, an important public health problem with high morbidity and mortality is functionally characterized by impaired contractile force, diminished intracellular Ca^{2+} cycling and dampened responsiveness to catecholamine stimulation. S100A1, a cardiac Ca^{2+} binding protein of the EF-hand type has been found to be significantly down-regulated in the failing myocardium but S100A1 protein overexpression in vitro has recently been shown to improve cardiac contractile performance. Thus, to prove the therapeutic potential for the concept of S100A1 gene-transfer in vivo, we assessed cardiac function and morphology in S100A1 transgenic mice (TG S100A1).
Methods/Results: C57/B6 TG S100A1 mice were generated by the use of the alpha-MHC promotor and hemodynamics were assessed in 6±1 month old TG S100A1 mice by cardiac catherization and echocardiography compared to non-transgenic littermate controls (NLC's). Contractility and whole-cell Ca^{2+} transients in isolated transgenic cardiomyocytes were investigated by edge-detection and FURA2-AM loading, respectively. Expression levels of S100A1, Ca^{2+} cycling proteins and β-AR were examined by Western-blotting. Adenylylcyclase(AC)activity was carried out in crude membrane preparations. A nearly 4-fold cardiac-restricted S100A1 protein overexpression significantly raised basal and isoproterenol-stimulated systolic and diastolic cardiac function in vivo as well as in isolated cardiac myocytes. In accordance, intracellular Ca^{2+} transients at baseline and in response to isoproterenol were found to be significantly enhanced by S100A1 overexpression while cardiac protein expression levels of DHPR, RyR, SERCA2a, PLB, NCX, CSQ and β1/2 receptors as well as cardiac AC activity remained unchanged. Despite the marked increase in cardiac performance, echocardiographic and biometric measurements revealed that S100A1 gene-tranfer did not lead to cardiac hypertrophy.
Conclusion: Our study clearly demonstrates for the first time that cardiac S100A1 gene-transfer in vivo is feasible and causes significantly increased cardiac contractile force at baseline and in response to β-adrenergic stimulation. No cardiomyopathic consequences occurred during the study period and cardiac response to β-adrenergic stimulation was preserved. These data are in line with our recent data of cAMP-independent increase in contractility in S100A1 overexpressing cardiomyocytes. Thus, cardiac S100A1 gene delievery may reverse impaired cardiac peformance of the failing heart and appears therefore as a novel inotropic strategy to treat symptomatic heart failure.

LEFT VENTRICULAR DYSFUNCTION: INSIGHTS FROM TRANSGENIC MICE

3344 Overexpression of phosphatase inhibitor-2 rescues the cardiac function defect of PP1c transgenic mice

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Background: In failing human myocardium, increased activity of protein phosphatases (PP) contributes to decreased phosphorylation of myocardial regulatory proteins resulting in impaired calcium handling and contractile dysfunction. The protein phosphatase 1 (PP1) has been implicated in the control of major regulators of cardiac function. However, the effect of cardiac specific overexpression or inhibition of the protein phosphatase has not been fully explored.
Methods: Mice with cardiac specific overexpression of the catalytic subunit of PP1 (PP1c OE) were crossed with mice overexpressing inhibitor-2 (PPI2 OE), an endogenous inhibitor of PP1c. Wild type (WT; n=6), PP1c OE (n=6), PPI2 OE (n=6) and PP1c/PPI2 OE (n=6) littermates six months of age were analyzed by biplane echocardiography and cardiac doppler using a 15 MHz transducer.
Results: PP1c OE mice showed decreased ventricular contractility. The fractional shorting (FS) and the velocity of circumferential shortening (Vcf) were lower in PP1c as compared to WT, PPI2 or PP1c/PPI2 OE mice (See Table). Ventricular contractility in PPI2 OE mice and in PP1c/PPI2 double transgenic mice was not significantly different from WT. Dilated cardiomyopathy was clearly present in PP1c OE mice. Left ventricular end-diastolic (LVEDd) and end-systolic (LVEDs) diameters were increased in PP1c OE vs. WT, PPI2 or PP1c/PPI2 OE animals. Left ventricular diameters in PPI2 OE and in double transgenic mice were not different from WT.

	WT	PPI2 OE	PP1cOE	PP1c/PPI2
LVEDd (mm)	4.8±0.2	4.5±0.1	5.6±0.3**	4.3±0.1
LVEDs (mm)	3.3±0.3	3.0±0.2	4.4±0.4**	2.9±0.1
FS (%)	31.4±2.5	34.8±2.1	22.9±2.5**	31.9±1.3
Vcf (circ/s)	5.1±0.4	4.9±0.4	3.6±0.4**	4.8±0.4

Values are given as mean ± SEM, n = 6 per group, ** indicates p<0.005)

Conclusions: 1) Overexpression of PP1c results in cardiac dilatation and impaired function and 2)additional overexpression of PPI2 rescues the PP1c defective phenotype. These results suggest that inhibition of protein phosphatases could provide a new target for therapeutic approaches in the prevention of heart failure.
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3345 Cardiac dilatation and impaired ventricular contractility in mice overexpressing protein phosphatase 2 (PP2A)

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Background: Impaired catecholamine-induced protein phosphorylation is a major determinant of cardiac function in heart failure. An increased activity of protein phosphatases has been described in failing human myocardium. Protein phosphatase 2A (PP2A) specifically targets e.g. to the cardiac ryanodine receptor and may therefore directly influence cardiac function.
Methods: We generated transgenic mice with cardiac specific overexpression of the catalytic subunit of PP2A. Age (16 weeks) and sex matched (10 female, 10 male) littermates were studied in sedation (ketamine and xylazine) via biplane echocardiography and cardiac doppler using a 15 MHz transducer.
Results: Heart rate (PP2A 334±14 vs. WT 317±13 bpm) and aortic flow (PP2A+ 10.1±1 vs. WT 8.9±0.6 ml/min) were maintained in PP2A+ mice. Left ventricular enddiastolic and endsystolic diameter, in contrast, were enlarged by 32%* and 55%* in PP2A+ mice. Cardiac contractility was depressed as evidenced by decreased fractional shortening (FS, 31% decrease*) and reduced velocity of circumferential shortening (Vcf, 25% lower*, *p<0.005). Values are given in mean±SEM.

Echocardiographic parameters

	WT	PP2A+
LVEDd (mm)	4.1±0.1	5.4±0.2*
LVEDs (mm)	2.7±0.1	4.1±0.3*
FS (%)	36±1	25±2*
Vcf(circ/s)	5.1±0.2	3.8±0.3*

Values are given in mean and SEM, n=10 per group, *=p<0.005.

Conclusions: Cardiac-specific overexpression of PP2A results in ventricular dilatation and reduced cardiac contractility in vivo. Increased activity of PP2A may contribute to impaired cardiac function in end stage human heart failure.

3346 Impaired SR Ca^{2+} uptake by a phospholamban mutant PLB/N27A is a sufficient primary cause of progressive left ventricular dysfunction and heart failure

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Increases in diastolic Ca^{2+} and impaired relaxation are associated with depressed sarcoplasmic reticulum (SR) Ca^{2+} uptake in end-stage failing hearts. However, the role of SR dysfunction in the onset and progression of heart failure is controversial. The present study tests the hypothesis that impairment of cytosolic Ca^{2+} sequestration by the sarcoplasmic reticulum via increased phospholamban inhibition, is a sufficient primary cause for left ventricular (LV) dysfunction and its progression to heart failure. A phospholamban Asn27 to Ala mutant (PLB/N27A), exhibiting a defined alteration in its three dimensional structure, as revealed by NMR analysis, was introduced in the cardiac compartment of the PLB null mouse. PLB/N27A expression (1-fold) resulted in a supershift of the EC50 value of the SR Ca^{2+} uptake (0.52±0.04* vs. 0.21±0.01 in wild-types: WT). Isolated cardiac myocytes and Langendorff-perfused hearts demonstrated preserved shortening fraction and peak systolic pressure development respectively; the rates of contraction (70%) and relaxation (53%) were significantly depressed compared to WTs. Furthermore, analysis of Ca^{2+} transients in Fura-2 loaded isolated myocytes showed significantly prolonged times for 80% Ca^{2+} signal decline (0.85±0.07*s vs. 0.52±0.07s in WT). Echocardiography revealed preserved fractional shortening (FS), but the isovolumic relaxation time was prolonged (48.2±6.7* ms vs. 25.8±1.9 ms in WT) and LV diastolic filling measured by the ratio of early to late LV filling (E/A) on transmitral Doppler was significantly impaired (1.09±0.09* vs. 1.76±0.1 in WT) in 12 week old PLB/N27A. Furthermore, a blunted force-frequency relation and an attenuated response to beta-agonist stimulation were observed in PLB/N27A hearts by LV-catheterization. Upon aging to 12 months, the predominantly diastolic dysfunction progressed to congestive heart failure, characterized by induction of a fetal gene program, cardiac remodeling, lung congestion and LV systolic dysfunction (FS %: 22.5±1.3* in N27A vs. 35.2±2.0 in WT). These findings suggest that changes in SR Ca^{2+} handling may be a primary causative factor rather than a compensatory response in the development of left ventricular dysfunction and the transition to heart failure. (* $P<0.05$.)

3347 Evaluation of left ventricular diastolic function from spectral and color M-mode Doppler in genetically altered mice

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Heart failure cause by abnormal diastolic function is far more common than previously recognized and its underlying cellular mechanisms are still poorly understood. Echocardiographic techniques have proven useful in determining the interplay between altered gene expression and physiological cardiovascular function in genetically altered mouse models. However, the role of non-invasive assessment of left-ventricular (LV) diastolic function in the intact mouse is unsettled. The objective of our study was to characterize patterns of LV diastolic function in two genetically altered mouse models using Doppler- and Color-M-mode echocardiography. Phospholamban (PLB) reversibly inhibits the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) and is a key regulator of myocardial relaxation. 12-week old PLB knock-out mice (PLB/KO) were examined in parallel with age-matched transgenic mice expressing a mutant form of PLB (PLB/N27A) that exhibited superinhibition of SERCA and compared to controls expressing wild-type PLB (WT) (n=14/group). LV-systolic function was preserved in PLB/N27A mice compared to WT as assessed by fractional shortening (FS) (see table). However, transmitral Doppler flow indexes, including isovolumic relaxation time (IVRT), the ratio of peak early-to-late filling velocities (E/A), and deceleration time of peak early transmitral velocity (DT) indicate impaired diastolic filling in the PLB/N27A mutants, but improved LV diastolic function in the PLB/KO mice. Additionally, a relatively load-independent parameter of LV relaxation measured by color M-mode Doppler, the propagation velocity of early flow into the LV cavity (Vp), was established in the mouse and used to confirm the observed differences. Inter- and intraobserver variability was very good.

Echo-parameters of LV function

	FS (%)	IVRT (ms)	E/A	DT (ms)	Vp (cm/s)
PLB/KO	41,9 ±2,3	17,2 ±2,1*	2,0 ±0,1*	24,9 ±1,7	70,8 ±10,8
PLB/WT	39,4 ±2,3	27,0 ±1,0	1,6 ±0,1	22,3 ±2,5	49,1 ±1,7
PLB/N27A	38,9 ±2,3	45,6 ±4,5*#	1,0 ±0,1*#	45,6 ±4,5*#	22,8 ±1,8*#

* $p<0,05$ vs. WT; # $p<0,05$ vs. PLB/KO

We conclude that transmitral filling patterns and color M-mode flow propagation velocity have the sensitivity to detect changes in myocardial relaxation in mice with genetically altered levels or activity of phospholamban and may be useful tools to characterize LV diastolic function in other mouse models of disease.

3348 Phospholamban ablation rescues intrinsic contractility but does not prevent remodelling in myosin-binding protein-C mutant mice

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Homozygous mice bearing mutated alleles of myosin-binding protein-C (MyBP-C/Neo) that encode a truncated peptide analogous to that found in human hypertrophic cardiomyopathy exhibit early dilated cardiomyopathy. To test the hypothesis that enhanced Ca^{2+}-cycling through the SR by phospholamban (PLB) ablation may improve cardiac dysfunction and prevent the progression of remodeling, we crossbred the PLB knock-out model (PLBKO) with the homozygous MyBP-C/Neo mouse and characterized the resulting double mutants (CROSS) (n=6/group). Isolated cardiac myocytes (table) from MyBP-C/Neo exhibited significantly depressed maximal rates of contraction (+dL/dt,μm/s), relenghtening (-dL/dt) and cell shortening (SF,%) compared to wild-type (WT), which was accompanied by a significantly prolonged Ca^{2+}-transient decay (time to 50% decay: T50, ms). Ablation of PLB (Cross) resulted in a full restoration of all depressed contractile and Ca^{2+} cycling parameters to levels even higher than those observed in WT littermates. However, PLB-ablation failed to significantly improve cardiac function in the intact animal, as assessed by echocardiography (fractional shortening (%); WT: 43,3±2,4; MyBP-C/Neo: 25,9±1,9*; CROSS: 30.8±2,7*) and LV-catheterization (-dP/dt (mmHg); WT:-9844±575; MyBP-C/Neo: -4367±64*; CROSS: 5536±167*). Furthermore, gravimetric analysis of myocardial hypertrophy, fetal gene markers and histopathological changes (myofibrillar disarray, fibrosis) show a similar degree of cardiac remodeling in MyBP-C/Neo and CROSS animals.

Isolated cardiomyocytes

* $p < 0,05$	+ dL/dt	-dL/dt	%SF	Ca^{2+}-Ampl.	T50
WT	128 ± 9	93 ± 14	11,7 ± 0,4	0,36 ± 0,02	326 ± 17
MyBP-C/Neo	86 ± 13*	45 ± 4*	8,8 ± 0,4	0,32 ± 0,02	410± 20*
CROSS	255 ± 28*	230 ± 29*	16,3± 2,3*	0,58± 0,05*	201 ± 15*

These results indicate that increased SR Ca^{2+} cycling by PLB ablation is able to rescue intrinsic contractility but not remodeling in MyBP-C/Neo mice, suggesting that deficits in force transmission may serve as the primary signaling-mechanism.

3349 Diastolic dysfunction and stress-induced cardiac decompensation in transgenic mice expressing the human troponin T (I79N) mutation

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The cardiac troponin T (TnT) I79N mutation is linked to familial hypertrophic cardiomyopathy and sudden death. To investigated LV pressure-volume relationships in transgenic mice expressing human wild type (Wt), human mutant TnT (I79N) and controls.. A micro-conductance catheter was introduced in the LV of anaesthetized (thiopental) and ventilated closed chest mice n =-8/group). During V. cava occlusion endsystolic and enddiastolic pressure volume relationships were obtained (ESPVR; EDPVR) under basal and stress conditions (0.25 mg/kg isoproterenol i.p.)

Basal: I79N mice showed increased systolic function compared to controls: EF: 63.3±.4.3* vs. 41.3±4.8%; SV: 35±3.2* vs. 26.5±2.3µl; CO: 16950±1300* vs. 10924±908 µl/min; Volume endsystolic: 26.55±2.3* vs. 43.6±5.6 µl; *p<0.05 without differences in HR, LVP and ESPVR-slope (Ees). LVEDP, Tau and PHT were unchanged, but the EDPVR-slope was increased (0.50±0.1* vs. 0.28±0.06; *p<0.05), indicating increased LV stiffness.

Stress: HR (654±21 vs. 675±12 bpm) and LVP (159.9±8.6 vs. 191.0±8.1* mmHg; *p<0.05) response was similar in all groups, but the systolic function of I79N mice decreased compared to controls (EF: 25.1±5.5* vs. 51.2±9.8%; SV: 13.97±3.28* vs. 23.13±1.76 µl; CO: 8916±1832* vs.14861±2887 µl/min; Ves: 42.22±3.67* vs. 26.57±7.21 µl and ESPVR-slope 2.35±0.57* vs. 4.3±0.78; *p<0.05). Diastolic indices demonstrate diastolic dysfunction in I79N compared to controls: LVEDP: 17.07±2.16* vs. 3.84±1.28 mmHg; *p<0.05 and PHT: 6.37±0.35* vs. 5.01±0.31 ms; *p<0.05. Increased EDPVR (1.12±0.34* vs. 0.47±0.09; *p<0.05) indicates cardiac stiffness worsened under b-adrenergic stimulation.

I79N TnT mice show an increased cardiac stiffness and diastolic dysfunction leading to decompensation under stress. These mice are a valuable model to study the mechanisms involved in humans with TnT mutations.

MOLECULAR MECHANISMS OF MYOCARDIAL ISCHAEMIA

3350 Involvement of free radicals and mitochondrial K+ATP channels in ischaemic preconditioning depends critically on the preconditioning stimulus

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The involvement of adenosine, mitochondrial ATP-sensitive potassium (KATP) channels and reactive oxygen species (ROS) in ischemic preconditioning remains incompletely understood. We previously observed in the in vivo rat heart, that adenosine contributes to ischemic preconditioning (IPC) produced by a single 15-min coronary artery occlusion (CAO) followed by 10 min of reperfusion (15-min CAO), but not to the cardioprotection afforded by 3 cycles of 3-min CAO interspersed by 5 min of reperfusion (3x3-min CAO). Adenosine-induced cardioprotection in the rabbit has recently been reported to be independent of ROS formation and mitochondrial KATP channel activation. Consequently, we investigated the involvement of mitochondrial KATP channels and ROS in the cardioprotection by the 15-min CAO and 3x3-min CAO preconditioning stimuli. Infarct size (IS) was determined measured after 120 min of reperfusion following a 60-min CAO in pentobarbital-anesthetized rats using trypan blue (negative staining of the area at risk) and nitro-blue-tetrazolium for vital staining. In control hearts IS comprised 70±1% (n=7) of the anatomical area at risk. IPC with a single 15-min CAO or 3x3-min CAO reduced IS to 47±3% (p<0.05, n=18) and 25±4% (p<0.05, n=16) respectively. The ROS scavenger MPG (1mg/kg/min iv), which had no effect on IS produced by 60-min CAO (IS = 68±2%, n=4) or on the cardioprotection afforded by 15-min CAO (IS = 39±7%, n=9), blunted IPC with 3x3-min CAO to 55±6% (n=10; p<0.05 vs 3x3-min CAO). In contrast, a high dose of the selective mitochondrial KATP channel blocker 5-hydroxydecanoate (5-HD, 20 mg/kg iv, followed by 20 mg/kg/h iv), which by itself had no effect on IS produced by a 60-min CAO (IS = 70±2%, n=3) or on IPC with 3x3-min CAO (34±8%, n=9), abolished IPC with a single 15-min CAO (71±3%, n=3).

In conclusion, a preconditioning stimulus consisting of a single 15-min CAO conferred cardioprotection via adenosine and mitochondrial KATP channels but did not involve the formation of reactive oxygen species. In contrast, 3 cycles of 3-min CAO, which afforded even more potent cardioprotection, involved increased formation of reactive oxygen species, but did not require adenosine or mitochondrial KATP channels. These findings indicate that preconditioning stimuli produce cardioprotection via markedly different signal transduction pathways.

3351 Cardioprotection and hypertrophy: role of STAT3 in a murine model of ischaemia and reperfusion

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Myocardial stress, such as pressure overload, ischemia and reperfusion, cause production of cytokines of the IL 6 family, which stimulate the JAK/STAT and the MAP kinase signal transduction pathways via the common receptor gp130. Overexpression of STAT3 in the heart leads to myocardial hypertrophy. However, the role of STAT3 in the heart can only be clarified by a conditional knock out, since the general STAT3 k.o. results in early embryonic mortality.

By crossing the aMHC-Cre transgene into the STAT3flox background a heart specific STAT3 k.o. mouse was generated. In this mouse the recombinase Cre is expressed under the control of the aMHC-promoter, which is only active in postnatal cardiomyocytes, thereby eliminating most of the function of the STAT3 gene in the adult heart (12 weeks of age) but not in other organs.

Under basal conditions aMHC-Cre;STAT3flox (STAT3-/-) mice do not show significant differences concerning mortality, bodyweight, heart morphology and function compared to wild type controls (WT). After ischemia/reperfusion (1h/7d) LV function as determined by echocardiography was significantly reduced in STAT3-/-animals compared to WT (FS 19% vs. 30%, p<0,05), and showed a significantly reduced hypertrophy (septum thickness +5% v.s. +32%, p<0,01; myocyte cross sectional area -11% v.s. +20%, p<0,01) as determined by morphometry. After 1h of ischemia followed by 24h of reperfusion, the STAT3-/- mice showed a 1,6 fold increase in infarct size as determined by Evans blue and TTC staining (p<0,01) associated with a 4 fold increase in TUNEL positive cells compared to WT (p< 0,001).

In conclusion cardiomyocyte specific knock out of STAT3 in mice shows no pathological phenotype under basal conditions. However, ischemia/reperfusion leads to subsequent LV dysfunction in STAT3 k.o. mice. This is possibly due to significant increase in infarct size with a marked elevation of apoptotic cells and is augmented by the lack of LV hypertrophy.

3352 Recombinant P-selectin glycoprotein ligand-Ig versus abciximab in conjunction with tenecteplase in a non-human primate model of thrombolysis

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We have shown that recombinant P-selectin Glycoprotein Ligand-Ig (rPSGL-Ig) with alteplase, reteplase or streptokinase accelerates thrombolysis and reduces acute reocclusion in porcine and canine models. In this study we evaluated rPSGL-Ig in conjunction with tenecteplase (TNK) and compared its efficacy to abciximab (abx). An occlusive thrombus was induced by placing a copper coil in the left femoral artery of 5-7 kg, male cynomolgus monkeys. All animals received aspirin and heparin was administered as follows: 70 U/kg bolus + 15 U/kg/hr in control and rPSGL-Ig animals, 60 U/kg bolus + 7 U/kg/hr in abx and abx + rPSGL-Ig animals. Animals received TNK 15 min post-occlusion as a 1.1 U/kg IV bolus followed by: (1) vehicle (2) rPSGL-Ig (500 µg/kg IV bolus) (3) abx (0.25 mg/kg IV bolus + 0.125 µg/kg/min infusion for the duration of the experiment) or (4) both rPSGL-Ig and abx. Antegrade blood flow was monitored by angiography every 10 min for 3 hr following TNK administration, and was scored on a scale 0-3. Bleeding times were measured on the forearm of the animals at baseline, 10 min after administering TNK and one of the 4 treatments above, and again prior to termination. Surgical and bleeding time site blood loss was recorded. In control monkeys, thrombolysis was achieved in 70±18.8 min (n=6). Both rPSGL-Ig and abx accelerated time to lysis by 64% (n=6; p=0.02) and 57% (n=5; p=0.05) respectively. The percentage of time that post-lysis blood flow was near-normal (score 2 or 3) was increased from 43.2±12.1% in control animals to 80±16.3% (p=0.05) and 83.6±14.7% (p=0.03) by rPSGL-Ig and abx respectively. The combination of rPSGL-Ig and abx was comparable to either agent alone. Bleeding times and surgical blood loss in rPSGL-Ig-treated animals were no different from control. Despite the lower dose of heparin, bleeding times in abx animals were significantly prolonged to greater than 10 min (when bleeding time measurement was terminated) at all times following abx administration. Surgical blood loss was increased from 16±7.4 g in control monkeys to 55.8±7.2 g in abx monkeys (p=0.002). Blood loss in monkeys receiving both rPSGL-Ig + abx (52.5±13.8 g) was no worse than with abx alone (p=0.85). These results suggest that rPSGL-Ig modulates platelet-leukocyte mediated thromboinflammatory events that result in tissue factor release, fibrin accretion, and contribute to thrombus amplification and stabilization. P-selectin blockade with rPSGL-Ig is as effective as platelet GPIIb/IIIa inhibition with abx in enhancing the efficacy of TNK, but without increasing bleeding complications.

3353 Aspirin prevents superoxide generation in acute myocardial ischaemia

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Background: Normal vascular homeostasis depends on endothelial elaboration of paracrine factors that prevent both platelet adhesion to the endothelial surface and inappropriate vasospasm. In vivo, .NO is subject to rapid inactivation by the superoxide anion, an obligate product of normal oxidative metabolism. Polymorphonuclear leukocytes (PMN) are integrated into the acute inflammatory response to tissue injury and possess the capacity to produce oxygen-derived free radicals such as superoxide anion, when activated by appropriate stimuli. It has been hypothesized that the protective anti-ischemic effects of aspirin (ASA), may be do not only to its anti-platelet, but to its anti inflammatory properties. To elucidate if ASA affects O2 generation - traces of PMN activity -18 anesthetized dogs were studied.
Methods: 18 dogs were subjected to 60 min of myocardial ischemia (MI) (LAD occlusion) and 30 min of reperfusion (RP). 9 dogs were pretreated with 500 mg of ASA, and were compared with 9 control (CT) dogs without ASA. We determined the risk/infarct area and relate it to the and to the .O2- generation (cytochrome c reduction/nmol/106 cells) of ex vivo phorbol ester-stimulated whole blood from both sets of dogs. Blood samples collected from the coronary sinus before LAD occlusion and 1,5,and 30 min after R.
Results: CT and ASA dogs presented similar infarcted areas (% risk areas): 38+4% and 35+1%, respectively. Results in the table are expressed as mean+SEM; *p<0.01, vs pre-occlusion; #p<0.04, CT vs ASA

	Pre-occl	1 min RP	5 min RP	30 min RP
.O2./CT	7+2	22+5*	30+4*,#	8+1
.O2./ASA	134+4	33+13*	51+8*	14+4

.O2./CT - superoxide anion generation in control dogs.O2./ASA - superoxide anion generation in aspirin trated dogs

Conclusion: Ex vivo O2 generation decreased significantly in stimulated cells suggesting in vivo activation. ASA, in addition to its anti-thrombotic effect, possesses an anti-oxidant effect.

3354 Effect of ischaemic preconditioning on oxygen radical production in myocardium: a microdialysis study with salicylate

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There is evidence that oxygen-derived free radicals play an essential role in the irreversible injury of cardiac cells associated with prolonged periods of ischemia. The aim of this study was to examine the effect of ischemic preconditioning on myocardial oxygen radical production using rat heart model of regional ischemia.
Methods: Experiments were carried out on anaesthized artificially ventilated open-chest male Wistar rats. The linear microdialysis probe was inserted in the left ventricle wall and perfused with Ringer solution containing sodium salicylate. 2,3-dihydrobenzoic acid (2,3-DHBA) produced in the reaction of oxygen radicals with salicylate was measured in dialysis samples by high-performance liquid chromatography. Before 30 min of coronary artery occlusion and 60 min of reperfusion, the hearts were either subjected or not subjected to preconditioning, which was achieved with three cycles of 5 min of ischemia followed by 5 min of reperfusion.
Results: In the control group, the regional prolonged ischemia induced a considerable increase of the 2,3-DHBA level (143±11% vs baseline) with maximum on 20-30 min of ischemia. Following reperfusion resulted in further extended rise of 2,3-DHBA level up to 214±18% (maximal level) after 20 min of reperfusion and 165±11% vs baseline value after 60 min of reperfusion. Preconditioning eliminated the increase of 2,3-DHBA level during prolonged ischemia and essentially restricted the elevated rate of oxygen radical production during reperfusion, which was observed only for the first 15 min of reperfusion. The changes in the kinetics of oxygen radical production were related to the limitation of the infarct size in preconditioned hearts – 5.4±1.4% vs 30.8±3.3% in control group. A worth mentioning finding of this study was the significant increase of the 2,3-DHBA level in preconditioned hearts during the second and third brief episodes of reperfusion (equal to 130±9% and 144±14% vs baseline level, respectively).
Conclusions: The results suggest that preconditioning significantly reduces the rate of oxygen radical production in myocardium during regional prolonged ischemia and reperfusion. It may play an important role in improvement of postischemic myocardial function. Oxygen radicals generated in cardiac myocytes during brief episodes of reperfusion may be involved in triggering of the cascade of protective mechanisms of ischemic preconditioning.

3355 Vascular stunning without myocardial stunning

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Background: Myocardial and vascular stunning coexist, but seem to represent relatively independent phenomena. For example, injury of endothelial cells precedes dysfunction of the cardiomyocytes.
Methods: To investigate uncoupling between myocardial and vascular stunning, experiments were performed on 31 isolated, blood-perfused rabbit hearts. Protocol: 30 min normoxia, 20 min no-flow ischemia, 60 min reperfusion. To assess vascular dysfunction, either placebo, an endothelium-independent NO-donor (SIN-1: 100 μM) or the endothelium-dependent vasodilator substance P (SP: 5 nM) was administered. This protocol was repeated in control hearts without ischemia/reperfusion.
Results: In the placebo group, ventricular function and coronary resistancec at the end of the protocol were not different from baseline. In the control hearts, SIN-1 and SP decreased coronary resistance by 35 and 39%, respectively. In the ischemic/reperfused hearts, the SIN-1-induced dilatation was almost maintained but the SP-induced dilatation was reduced to 9% (p<0.05 vs controls). In the three groups, postischemic/reperfused systolic ventricular function was not significantly reduced compared with baseline.
Conclusions: Our results convincingly show that brief global ischemia and reperfusion in isolated rabbit hearts can induce vascular (endothelial) stunning without impairing myocardial function (myocardial stunning). Thus, the absence of a postischemic contractile dysfunction does not ensure the absence of postischemic injury.

THROMBOLYTIC "COCKTAILS" – BENEFICIAL OR DANGEROUS

3356 Half dose lytic plus abciximab compared to full dose lytic in acute myocardial infarction: a meta-analysis

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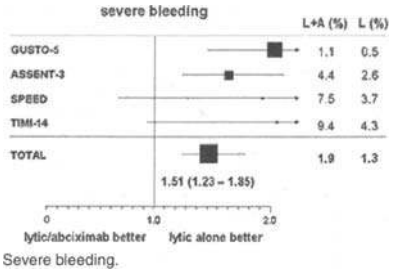
Background: Angiographic trials have shown improved 60 and 90 minutes coronary patency with half-dose lytic plus abciximab versus lytic alone in ST-elevation MI (STEMI). These strategies have recently been evaluated in 2 phase III megatrials for efficacy and safety.
Methods: Rates of 30-day mortality, intracranial hemorrhage (ICH), severe extracranial bleeding and transfusions were collected from the half-dose lytic plus abciximab arms and the lytic alone arms of TIMI-14 and SPEED, and the megatrials GUSTO-V and ASSENT-3.
Results: In total 23,322 patients were randomized in these 4 published trials: 10,713 in the half-dose lytic plus abciximab groups and 12,609 in the lytic alone groups. 30-day death was similar in both groups: 5.8% vs 5.8% (RR 0.99, 95%CI 0.81-1.10, p = 0.88) as was the rate of ICH: 0.7% vs 0.7% (RR 0.98, 95%CI 0.49-1.96, p = 0.96). But, severe extracranial bleeding was very significantly increased by half-dose lytic plus abciximab (L+A) compared to lytic alone (L, figure), as was the need for transfusion: 5.6% vs 3.9% (RR 1.46, 95%CI 1.30-1.64).



Severe bleeding.

Conclusion: In comparison to a fibrinolytic alone, reduced dose fibrinolytic combined with abciximab for STEMI significantly increases severe bleeding and transfusion with 50% without reducing mortality or hemorrhagic stroke. This costly combination should be avoided as a routine, and trial designs evaluating the combination for facilitated primary PCI or for prehospital/ER use prior to primary PCI should be reconsidered.

3357 Age and risk of intracranial haemorrhage with abciximab and half-dose reteplase in acute myocardial infarction: dichotomous response in the GUSTO V trial

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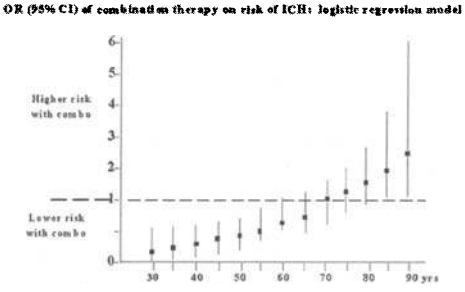
By reducing the dosages of the fibrinolytic agent and heparin, combination therapy with a GPIIb/IIIa blocker, half-dose lytic and reduced-dose heparin has the theoretic potential for reducing the risk of intracranial hemorrhage (ICH) associated with thrombolytic treatment of acute MI. We evaluated the relation between univariate and multivariate predictors of ICH and the efect of treatment with either abciximab and half-dose reteplase (combination therapy) or reteplase alone in the 16588 patients randomised in the GUSTO V trial. Overall, the incidence of ICH was similar in the two groups (0.6% vs 0.6%: OR 1.05, 95% CI 0.71, 1.56). Among the multivariable predictors of ICH, only age showed a significant interaction with treatment effect (age per treatment interaction Chi-square 7.103, P=0.008). When the age per treatment interaction is not included in the logistic regression model (C statistic 0.828), treatment with combination therapy is nonsignificant in predicting ICH. However, when the interaction term is included (C statistic 0.822), combination therapy becomes a significant predictor (Chi-square 6.953, P=0.008). The relationship between age and the odds ratio of having an ICH for patients randomised to combination therapy compared to reteplase alone is shown in the figure: a significant lower risk of combination therapy is observed for people of age <57, and a significantly higher risk for people >82.



ICH and age.

Thus, although no additional risk of ICH exixts with combination therapy in the whole population, a significant age per treatment interaction exixts, with a protective effect from combination therapy in younger patients and a higher risk in the elderly.

3358 Combination eptifibatide and reduced-dose tenecteplase in acute ST-segment elevation myocardial infarction: final results of a phase II angiographic trial (INTEGRITI)

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Background: Prior studies suggest combination glycoprotein IIb/IIIa inhibition and reduced-dose fibrinolytic may restore infarct artery patency and tissue perfusion more effectively than fibrinolytic monotherapy.
Methods: 438 patients with STE-MI (median age 58y, 77% men, 33% anterior MI) were treated with aspirin and heparin. In dose-finding 189 patients received one of three combinations of eptifibatide (ept) and tenecteplase (TNK): 1)ept 180/2/90 + 50%TNK, 2)ept 180/2/90 + 75%TNK, 3)ept 180/2/180 + 50%TNK. In dose confirmation, 249 patients received either ept 180/2/180 + 50%TNK vs. full-dose (0.53 mg/kg) TNK monotherapy. The primary endpoint was the rate of TIMI 3 epicardial flow at 60 min as determined by a blinded angiographic core laboratory.
Results: TIMI 3 flow rates with the three combinations of ept+TNK in dose confirmation were similar (64-68%), while arterial patency was highest (96%) with ept 180/2/180 + 50%TNK. In dose confirmation, ept 180/2/180 + 50%TNK compared to TNK alone achieved higher rates of TIMI 3 epicardial flow (59% vs 49%, p=0.15), arterial patency 85% vs 77% (p=0.17), and faster median corrected TIMI frame count (36 vs 40 frames, p=0.54). Myocardial perfusion was improved with combination therapy as determined by median ST-segment resolution (71% vs 61%, p=0.08), and rate of TIMI myocardial perfusion grade 3 flow (49% vs 45%, p=0.59). At 48 hours and 30 days, combination therapy tended to have lower rates of death (48h: 1.7% vs 4.2%, p=0.25; 30d: 3.4% vs. 5.1%, p=0.51) and of the triple composite death+MI+urgent target vessel revascularization (48h: 3.4% vs. 11.0%, p=0.02; 30d: 10.9% vs. 14.4%, p=0.42). More major hemorrhage (7.6% vs. 2.5%, p=0.14) was seen with combination therapy, however this was all non-cerebral bleeding.
Conclusions: Ept 180/2/180 + 50%TNK improves epicardial and myocardial reperfusion, although it may also increase non-cerebral bleeding. This combination is being evaluated in a phase III study (ADVANCE-MI), with minor modifications aimed at reducing bleeding.

3359 TNK with reduced dose unfractionated heparin associated with similar efficacy and less bleeding: results from ASSENT-2 and ASSENT-3

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Background: ACC/AHA guidelines for management of acute MI call for weight-based, reduced-dose unfractionated heparin (UFH) with fibrinolytic therapy, however, this regimen has never been prospectively tested. We compared outcomes of patients receiving TNK-tPA and the current ACC/AHA-regimen UFH in ASSENT-3 and the former standard UFH regimen in ASSENT-2.
Methods: The ASSENT-2 and ASSENT-3 trials had similar inclusion criteria. In ASSENT-3, 2038 patients received TNK, a 60 U/kg bolus (max. 4000 U), and 12 U/kg/hour (max. 1000 U/hr) initial infusion of UFH. In ASSENT-2, 8461 patients received TNK and UFH. Those weighing >67 kg received a 5000 U UFH bolus and 1000 U/hour initial infusion and those weighing <67kg received 4000 U bolus and 800 U/hour initial infusion. In both trials, UFH was adjusted to an aPTT of 50-70 seconds. In ASSENT-3, a 3 hour aPTT was added to allow early adjustment for aPTT >70 seconds. We compared outcomes before and after adjusting for baseline predictors of 30-day mortality (age, systolic BP, heart rate, MI location, Killip class) and major bleeding (age, gender, weight, diastolic BP, HTN, region).
Results: ASSENT-3 and ASSENT-2 patients had similar baseline characteristics. Those in ASSENT-3 underwent less CABG (5.2% vs. 5.5%) and more PCI (31% vs. 24%) than those in ASSENT-2. Outcomes are shown in the Table. Adjusted 30-day mortality was similar in ASSENT-3 and ASSENT-2 (OR 0.96, p=0.73) but the adjusted risk of major bleeding in ASSENT-3 was lower (OR 0.45, p<0.001).

Outcome	ASSENT-3 (n=2038)	ASSENT-2 (n=8461)	p-value
Death (30d)	6.0%	6.2%	0.77
Death (30d)/MI	9.6%	9.5%	0.96
Death (30d)/MI/RI	17.5%	17.0%	0.60
ICH	0.93%	0.93%	0.88
Major Bleeding	2.2%	4.7%	0.001
Transfusion	2.3%	4.3%	0.001

Conclusion: These data support the use of ACC/AHA guideline recommended weight-based, reduced-dose UFH regimen with fibrinolytic therapy. This regimen results in less systemic bleeding but similar ICH compared to more aggressive UFH dosing, with no loss of efficacy.

3360 Combination therapy with reduced-dose tenecteplase and eptifibatide results in faster and more stable reperfusion for acute myocardial infarction

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Background: Despite improved infarct-artery patency with reduced-dose fibrinolytics and glycoprotein (GP) IIb/IIIa inhibitors, combination reperfusion therapy has not improved survival in patients with acute myocardial infarction (MI). Further characterization of the timing of reperfusion may elucidate the paradoxical impact of combination therapy on surrogate biomarkers of reperfusion and clinical outcomes.
Methods: The INTEGRITI trial was a dose-ranging, phase II trial evaluating reduced-dose tenecteplase and eptifibatide in patients with acute ST-elevation MI. Patients from North American sites were included in a continuous ST-segment monitoring substudy for 24 hours using digital 12-lead Holter sampling of the electrocardiogram every 60 seconds (Rozinn 152). Patients who received combination therapy with 50% of the standard tenecteplase dose (0.5 μg/kg) and eptifibatide (180 μg/kg double-bolus with a 2.0 μg/kg/min continuous infusion) were compared to patients who recieved full-dose tenecteplase monotherapy. ST recovery parameters were based upon the timing of stable ST resolution (>= 50%) and the presence of any ST re-elevation in the lead with peak ST elevation.
Results: ST-recovery parameters are listed in the table. Continuously updated ST recovery analyses demonstrated greater ST-resolution in the combination therapy group at 30 minutes (57.7% vs. 43.8%), 60 minutes (82.7% vs. 65.6%), and 90 minutes (90.4% vs. 78.1%).

Variable	Full-Dose TNK (n = 45)	50% TNK + Eptifibatide (n = 73)	p-value
Time to Stable ST Resolution (mins)	98 (0,148)	55 (0,95)	0.058
Stable ST Resolution by 2 hrs (%)	67.7	89.4	0.016
ST Recovery Curve Area (uV/min)	4858 (598,13721)	1710 (0,4156)	0.020
Recurrent Ischemia (%) *	57.1%	34.0%	0.050

*Includes cyclic flow and late ST-segment re-elevation after initial ST resolution. TNK, tenecteplase.

Conclusions: Combination therapy with reduced-dose tenecteplase and eptifibatide accelerates early reperfusion and reduces the risk of recurrent ischemia in patients with acute MI. These results suggest that combination therapy may improve myocardial salvage, but further studies are needed to delineate the impact of this benefit on clinical outcomes.

3361 Influence of enoxaparin and early revascularisation on death or myocardial infarction after thrombolysis in myocardial infarction

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The ASSENT-3 trial showed that enoxaparin (Enox; n=2040) or abciximab + heparin (n=2017) in comparison to the standard treatment with unfractionated heparin (UFH; n=2038) reduced in-hospital rates of death or myocardial infarction (MI) - 6.8, 7.3% versus 9.1% (p=0.016). We evaluated the two heparin arms concerning the risk of occurrence of these events after discharge as enoxaparin treatment was terminated either at in-hospital revascularisation (revasc.) or at discharge (disch.)
Methods: The ASSENT-3 trial randomised ST-elevation MI patients in 25 countries to fibrinolytic treatment with TNK-tPA and either 48 hours infusion of UFH (APTT 50-70 sec) or s.c. Enox b.i.d. (1 mg/kg b.w.) until revascularisation or hospital disch - maximum 7 days. The primary end-point was a composite of 30-days mortality and in-hospital myocardial infarction or severe ischemia. Myocardial infarction from disch. until 30-days follow-up was collected as readmissions caused by reinfarction. In-hospital revasc. was at the discretion of the physician and varied from 2 - 72% between the countries.
Results:

Results death + MI	n/n	UFH	Enox	p
All: In-hospital	2038/2040	9.1%	6.8%	0.006
All: Entry - 30d	2038/2040	10.5%	9.1%	0.14
Revasc: Disch-30d	673/623	1.0%	1.3%	0.68
No revasc:Disch-30d	1210/1282	1.9%	3.3%	0.031

In multivariate analyses in hospital revasc. was significantly associated with a lowered (p=0.005) risk of death or MI after hospital discharge after adjusting for age, diabetes, infarct size and medication.
Conclusion: Revascularisation early after thrombolysis of acute ST-elevation MI seems associated with a reduced occurrence of death or myocardial infarction and to contribute to maintain the long-term benefits of adjuvant treatment with enoxaparin.

GLYCOPROTEIN IIB/IIIA – NEW ASPECTS

3362 Troponin release in patients with unstable angina – Relation to platelet aggregability and PLA2 polymorphism

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The glycoprotein IIb/IIIa receptor (GP IIb/IIIa) plays a pivotal role in platelet aggregation. Recent data suggest that the PlA2 polymorphism (GP IIIa subunit) is associated with an adverse outcome. However, it is unknown for patients with unstable angina whether there is an association between PlA2 polymorphism, platelet reactivity, and Troponin T (TnT) release. **Methods and Results:** We prospectively studied the TnT status, the GP IIIa genotype (PCR-based restriction fragment length polymorphism analysis), and the platelet reactivity (P-selectin expression, circulating monocyte-platelet aggregates) in 125 patients with unstable angina. TnT elevation > 0.1 ug/L was observed in 37% of the patients. At least one PlA2 allele was present in 24.5% of the patients whereas for TnT-positive patients at least one PlA2 allele was present in 53.7% of the patients. The PLA2 polymorphism was associated with increased platelet aggregability as indicated by increased P-selectin expression (74.9% versus 52.4%; PLA2 vs. PLA1; $P<0.01$) and increased number of circulating monocyte-platelet aggregates (32.9% versus 19.8%; $P<0.01$). TnT elevation was also highly predictive of increased platelet reactivity as indicated by P-selectin expression (72.5% vs. 48.1%; TnT pos. vs. TnT neg.; $P<0.01$) and circulating monocyte-platelet aggregates (38.2% vs. 16.9%; $P<0.01$). Consequently, a high correlation was observed between genotype and TnT elevation ($r=0.63$; $P<0.001$). However, in a multivariate analysis, TnT elevation, but not PLA2 polymorphism, was an independent predictor of platelet activation ($P<0.001$).
Conclusions: Our findings indicate that molecular variants of the gene encoding GP IIIa play a role in platelet reactivity. In patients with unstable angina, TnT appears to be a powerful surrogate marker for platelet hyperreactivity. Our observations are compatible with and provide an explanation for the reported predominant benefit of GP IIb/IIIa receptor antagonists in patients with elevated TnT levels.

3363 Influence of glycoprotein IIb/IIIa antagonist abciximab on platelet induced monocyte tissue factor expression

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Background: Tissue Factor (TF), the major physiological initiator of the coagulation cascade is normally not expressed by cells within the circulation. However, activated platelets induce monocyte TF expression. We studied the effect of abciximab, a glycoprotein IIb/IIIa antagonist used in percutaneous coronary interventions (PCI), on platelet-monocyte cross talk and monocyte TF expression in vitro. **Methods:** Expression of TF as well as total (CD42) and activated (CD62P, CD40 Ligand) platelet load was determined on CD14 positive monocytes by a four colour whole blood cytometric technique after stimulation with thrombin receptor agonist (TRA; 12.5μM) in the absence or presence of abciximab (50μg/ml). Whole cell procoagulant activity was assessed in a chromogenic assay. **Results:** Percentage of activated platelets (CD62P) on monocytes correlated positively with total monocyte platelet load (CD42; $r=0.97$, $p<0.001$) and CD40 Ligand after stimulation ($r=0.90$, $p<0.001$). TF mean fluorescence intensity (MFI) was positively correlated with platelet activation measured by CD62 MFI in timecourse ($r=0.75$, $p<0.001$) TRA stimulation resulted in a significant increase in monocyte TF expression ($p<0.001$), whereas preincubation with abciximab abolished this effect ($p=0.3$) and significantly reduced TF after 1, 5, 10 and 30 minutes (see table). Abciximab preincubation significantly lowered percentage of CD62 expression on platelet-monocyte aggregates after TRA stimulation ($p<0.05$). Similarly, whole cell procoagulant activity was decreased with abciximab pretreatment ($p<0.05$).

	0 min	1min	5min	10min	30min	60min
TRA	12.9 ± 3.3	33.0 ± 9.2	25.2 ± 12.1	28.9 ± 11.9	37.2 ± 8.7	37.4 ± 13.8
TRA+abcixmab	12.9 ± 3.3	13.6 ± 7.1	12.6± 5.8	15.4 ± 8.9	15.4 ± 10.5	20.2 ± 14.3
p-value	1.0	0.001	0.04	0.018	0.002	0.069

Percentage of TF positve monocytes (mean±std) in timecourse after TRA stimulation w/o abciximab (n=6)

Conclusion: We demonstrate reduced TF expression and procoagulant activity due to altered total and activated platelet load on monocytes by abciximab. Next to inhibition of platelet aggregation this my further contribute to the efficacy of abciximab in preventing thrombotic complications in PCI.

3364 Eptifibatide blocks the increase in C-reactive protein levels induced by coronary angioplasty

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Background: The increase in C-reactive protein levels usually observed after coronary angioplasty has been thought to be produced by an increased inflammatory response to lesion dilatation. However, this inflammatory response could be initiated by the high intraarterial thrombogenic activity induced by balloon-produced plaque fracture.
Methods: We measured C-reactive protein levels by nephelometry in patients with coronary angioplasty after blocking thrombosis by means of a selective platelet GP IIb-IIIa receptor antagonist. Ninety patients who underwent a coronary angioplasty procedure at our cardiac catheterization laboratory were included. We excluded patients with recent myocardial infarction, recent surgery or inflammatory, metabolic or neoplastic diseases. C-reactive protein was determined pre angioplasty, 24 and 48 hours after the procedure. In 48 patients Eptifibatide perfusion was initiated immediately after the procedure, and continued for only 24 hours.
Results are shown in the table.

C-reactive protein after PTCA

	n	Pre-PTCA	24 h	48 h
Eptifibade	48	0.41(0.48)	0.41(0.65)	0.95(0.89)**
Control	42	0.52(0.44)	1.16(0.98)*	1.62(1.45)**
p		ns	p<0.001	p<0.01

PTCA: Percutaneous coronary angioplasty. Numbers are: mean(SD);* p<0.05 to Pre-PTCA; ** p<0.05 to 24 h.

Conclusions: Eptifibatide, a synthetic peptide, which is a selective blocker of the platelet GP IIb-IIIa receptor with no known anti-inflammatory effects, significantly blocked C-reactive protein concentration elevation after angioplasty. C-reactive protein increased again after Eptifibatide perfusion was interrupted. These results suggest that arterial thrombosis may trigger the incresase in C-reactive protein elevation after coronary angioplasty.

3365 Glycoprotein IIb/IIIa antagonists and inflammation: a new effect mechanism in patients with unstable angina pectoris

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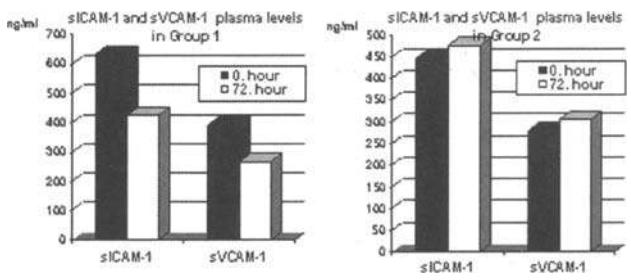
Aim: Inflammation has an important role in the pathogenesis of unstable angina pectoris (UAP). The anti-inflammatory effect of Tirofiban, glycoprotein IIb/IIIa antagonist, was evaluated in patients with UAP.
Methods: This study compares changes in level of intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) between patients receiving tirofiban (Group 1: n=15) or placebo (Group 2: n=20) in addition to heparin and aspirin for treatment of an UAP. Blood samples were drawn at 0 hour and 72 hour. 10 patients with stable coronary artery disease (Group 3) and 10 patients with normal coronary angiography (Group 4) were selected as control groups.
Results: Circulating venous plasma sICAM-1 and sVCAM-1 (p<0.0001) levels were higher in the UAP patient group (Group 1,2) than the control groups. In Group 1, sICAM-1 and sVCAM-1 (p<0.0001) levels decreased significantly as compared with the baseline (table).

Group		Mean	Std. Dev.	p
1	Pair 1 sICAM-1(0h)-sICAM-1(72h)	209.6	139.2	0.000
1	Pair 2 sVCAM-1(0h)-sVCAM-1(72h)	121.6	50.9	0.000
2	Pair 1 sICAM-1(0h)-sICAM-1(72h)	-29.8	109.9	0.24
2	Pair 2 sVCAM-1(0h)-sVCAM-1(72h)	-25.7	51.2	0.037

In Group 2, sICAM-1 (p:0. 24) and sVCAM-1 (p<0.037)levels were remained unchanged or increased (figure).



Conclusion: After the Tirofiban infusion, inflammatory response decreased significantly in patients with UAP.

3366 Effects of roxifiban on platelet aggregation and major receptor expression in patients with coronary artery disease

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Background: It has been expected that therapy with oral GPIIb/IIIa blockers including roxifiban will reduce mortality and vascular complications in a long-term. However, platelet-related properties of roxifiban in the clinical setting are not well known. We measured platelet characteristics during chronic treatment in patients with coronary artery disease enrolled in the Roxifiban Oral Compound Kinetics Evaluation Trial (ROCKET-I).
Methods: ROCKET-1 was designed as a randomized, double blind, multicenter, dose-ranging study of roxifiban, administered either as monotherapy or concomitantly with aspirin compared to aspirin alone. Thirty-one patients were assigned for 24 weeks of therapy with aspirin (n=7), roxifiban (n=9), roxifiban+aspirin (n=15). Platelets were assessed five times in each patient at baseline, and at week 2, 4, 12, 18, 24 thereafter by aggregometry, and flow cytometry.
Results: Baseline platelet characteristics were similar between all three groups. There was a consistent significant decrease of ADP- (p=0.0001), and collagen-induced (p=0.002) platelet aggregation in the roxifiban-treated patients when compared with those treated with aspirin alone. Flow cytometry revealed paradoxical late activation of GP IIb/IIIa expression (p=0.007) when roxifiban was used without aspirin which was significant compared to aspirin, and aspirin-roxifiban groups. There were no differences among groups in GP Ib expression, although it's rise was more profound in the roxifiban-treated patients. There were substantial differences in the P-selectin expression. While aspirin time-dependently decreased per cent of P-selectin positive platelets (p=0.02), treatment with roxifiban resulted in the phasic changes with the early inhibition (p=0.01), and then two-fold activation (p=0.0001) starting at week 12 of the therapy. There was an early transient activation of PECAM-1 expression (p=0.008) at week 2, followed by the later inhibition of this receptor (p=0.003) in patients treated with roxifiban.
Conclusion: Despite achieving sustained inhibition of platelet aggregation, therapy with roxifiban has been associated with over expression or phasic changes of major platelet receptors. These data may explain clinical concerns with the use of oral GPIIb/IIIa inhibitors linking higher mortality rates and incidence of thrombotic episodes with paradoxical switching to alternative passways of platelet activation.

3367 Selection of human single chain antibodies against the activated conformation of GPIIb/IIIa from a natural and a synthetic phage library

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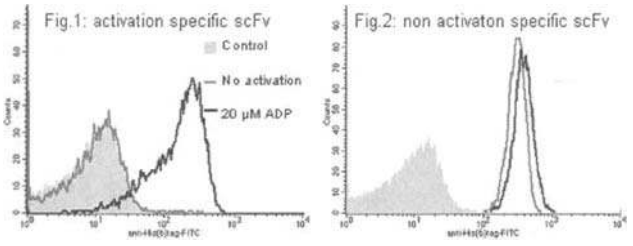
All GPIIb/IIIa-blockers, which are currently in clinical use are binding to the receptor irrespectively to its conformational state. However an activation- specific blocker might provide several advantages, such as decreased bleeding complications and less induction of ligand-induced binding sites.
Therefore we used phage display to obtain activation-specific single chain antibody fragments(scFv) from two different libraries: A natural library was constructed using cDNA from human lymphocyte donors encoding heavy and light chains of antibodies. These sequences were assembled in the phagemid vector pEXHAM1. A synthetic library was constructed by introduction of a randomised nucleotide-sequences in the CDR3 region of a constant framework scFv-sequence. As target for the selection we used activated GPIIb/IIIa on ADP-stimulated platelets and GPIIb/IIIa on transfected CHO-cells bearing a GFFKR-Deletion. The various resulting clones were expressed in the periplasmic space of E.coli and screened in flow cytometry, using an FITC-labelled anti-His(6)-tag antibody. In addition to some non-activation-specific antibodies (see fig. 2), more than 8 activation-specific were obtained from both libraries. These activation-specific antibodies demonstrate nearly no binding to non-activated platelets,which is 3 to 8 fold increased on ADP-stimulated platelets (see figure).



Distinct activation specifities of scFv.

In analogy to the GPIIb/IIIa-binding-sequence on fibrinogen the CDR3-regions of nearly all activation specific scFv's demonstrated RXD-sequences.The obtained scFv-sequences might help to improve the understanding of the function of GP IIb/IIIa and its interaction with ligands and blockers. Moreover, these newly generated human scFv-antibodies may represent a new class pharmaca for an advanced GPIIb/IIIa-blockade.

PERCUTANEOUS CORONARY INTERVENTION IN 2002: ACHIEVEMENTS, HOWEVER, SOME DARKNESS REMAINS!

3368 Coronary artery perforations: incidence, predictors and clinical outcome

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Background: Coronary perforation is an uncommon but potentially life-threatening complication of percutaneous coronary intervention (PCI). The aim of the present study was to determine the incidence, associated factors, in-hospital and late outcome of patients sustaining a coronary perforation.
Methods and Results: Between 4/1993 and 11/2001 5728 patients with 10000 lesions were treated in our institution with different PCI modalities (2838 angioplasty - POBA, 6836 coronary stenting, 444 directional coronary atherectomy - DCA, 518 rotational atherectomy - ROTA, 48 laser angioplasty and 637 cutting balloon, 25 other new devices, including overlap). Clinical, procedural and angiographic characteristics were compared between patients with ruptured vessels and overall population.
Coronary perforations occurred in 84 patients (1.47%) and were graded according to Ellis classification (56 class 2 and 28 class 3). Perforation occurred during: POBA 45 (53.6%), DCA 8 (9.5%), ROTA 3 (3.6%), cutting balloon 2 (2.4%), guidewire manipulation 23 (27.4%) and other devices 3 (3.6%). Treatment: CABG 11,prolonged inflation 36, stenting 20 (PTFE covered stent 10), only protamin administration 17 perforations. None of clinical variables correlated with perforation occurrence, although trend was observed for women (2.13% vs. 1.36%, p=0.09). Perforations were more commonly observed following atheroablative procedures (2.4% of 639 procedures vs. 1.3% of 5005 non-atheroablative procedures, OR=1.8, 95%CI 1.1-3.2, p=0.027) and there was a trend for use of platelet GP IIb/IIIa inhibitors (2.6% vs. 1.4%, p=0.06). Perforations occurred more frequently when complex lesions were treated (1.9% vs. 0.5%, OR=3.6, 95%CI 1.8-7.2, p=0.001) and higher balloon-to-artery ratio used (1.29±0.25 vs. 1.19±0.31 mm, OR=7.6, 95%CI 2.8-20.7, p=0.001).
In-hospital outcome: 27 patients had major adverse cardiac events (32.1%). 15 patients (17.8%) had myocardial infarction (MI) (8 non-Q-wave MI and 7 Q-wave MI), 11 patients (13.1%) underwent emergency CABG and 7 patients died (8.3%). All patients who underwent emergency CABG or died had class 3 perforation.
Late outcome: Clinical follow-up was performed for all 77 eligible patients after 33±28 months. Six patients (7.8%) died, 8 patients (10.4%) underwent CABG and two patients (2.6%) had Q-wave MI.
Conclusions: Coronary perforations occurred more frequently in patients with complex lesions, higher balloon-to-artery ratio and following atheroablative procedures. Class 3 coronary perforation carries a high incidence of adverse outcome, including death.

3369 Predictors for thrombotic events within the first month after stent placement in small coronary arteries

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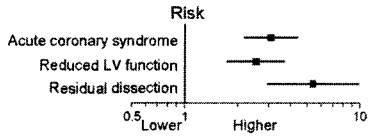
Thrombotic stent occlusion leading to myocardial infarction or death is a severe complication within the first month after stent placement. Stent placement in small coronary arteries (<3.0mm) represents an increasing proportion of the stent placement procedures each year. The purpose of this study was to investigate the predictors of thrombotic events occurring within 30 days after the procedure including also the role of stent design.
Methods: Successful stent placement in small coronary arteries was performed in a consecutive series of 3112 patients. All patients received the combined antiplatelet therapy with aspirin and ticlopidine/clopidogrel for 4 weeks. Thrombotic events were defined as death, myocardial infarction or stent occlusion documented by angiography.
Results: The cumulative thrombotic event rate was 4.2%. The figure demonstrates the three strongest predictors for thrombotic events. Stent design which is an important predictor for long-term outcome in small coronary arteries, was not identified as significant risk factor for early thrombotic events (P=0.38).



Risk for thrombotic events.

Conclusions: Early thrombotic complications occurred in a low percentage of patients in this large, unselected population. The predictors for thrombotic complications are predominantly clinical factors, indicating the need of a pre-interventional risk stratification with an intensified antithrombotic regimen for high risk patients. Although the stent design has a major impact on the angiographic and clinical long-term outcome, this analysis demonstrates that early thrombotic events are not influenced by differences in stent design.

3370 Ventricular fibrillation during coronary angiography/angioplasty: an incidental event or a prognostic marker?

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Background: Ventricular Fibrillation (VF) during coronary angiography/angioplasty (CA) is a known phenomenon, attributed to various etiologies and perceived as an innocent event. There are no data of the impact of this event on prognosis.
Aim: To analyze the prognostic implications of VF during CA.
Methods: Analysis of 5328 CA procedures performed at our institute revealed 25 cases of VF. The clinical characteristics, indications, co- morbidity factors, type of procedure, time to mortality of the VF patients (pts) were analyzed and compared to 201 matched controlled CA pts. without VF. Non-ionic/low osmolarity contrast media was routinely used in all the acute/unstable pts.
Results: Analysis of multiple demographic, clinical and technical procedure parameters did not reveal any significant differences between the VF and non-VF pts.
DM, COPD and use of IIb IIIa inhibitors was higher among VF pts ($p<0.05$). The mortality of VF vs. non-VF pts was 40% vs. 14%, respectively (p=0.001), during follow-up of 10.4+17.8 m. Mortality 24 hours post CA was 24% in the VF pts vs. 5.8% in the non-VF pts (p=0.001). The in hospital mortality among the VF pts that underwent CA during acute MI or cardiogenic shock was 50% (6/12). The mortality of the elective pts with VF during CA was 31% (4/13).
Conclusions: VF during CA seems to be a prognostic marker for mortality. It implications should be viewed beyond incidental occurrence related to mechanical events or contrast material osmolarity. Therefore those pts should be evaluated and treated as high-risk pts.

3371 Prevention of renal function worsening by haemofiltration in patients with chronic renal failure undergoing percutaneous coronary interventions

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Radiocontrast exposure and hemodynamic instability during percutaneous coronary interventions (PCI) are significant causes of renal dysfunction that can require hemodialysis (HD), particularly in patients with pre-existent renal insufficiency. Treatment with HD is associated with poor outcomes, including a 40% in-hospital mortality rate. Therefore, a preventive strategy targeted for beneficial outcomes is an important challenge; however, no effective measures have been found. We investigated the role of continuous veno-venous hemofiltration (CVVH), as compared with isotonic hydration, in preventing radiocontrast nephropathy in high-risk patients. Indeed, CVVH allows: 1) high-volume, controlled hydration before and after exposure to contrast agent, 2) removal of dye from the circulation resulting in reduced kidney exposure, 3) intravascular volume stability. Seventy-five consecutive patients with chronic renal insufficiency (serum creatinine > 2 mg/dl) undergoing PCI, were submitted to either percutaneous (Y-shaped double lumen catheter inserted in a femoral vein)CVVH (n=41; 37% diabetes; baseline creatinine = 3.1±1 mg/dl) or to conventional treatment (n=34; 35% diabetes, baseline creatinine = 3.0±1 mg/dl) with isotonic saline at a rate of 1 ml/kg/hour. CVVH (fluid replacement rate of 1000 ml/hr without weight loss) was started 9±10 hours before and continued 24 hours after PCI. Saline hydration was started one day before and continued 24 hours after PCI. The mean radiocontrast volume was 270±140 ml in CVVH patients and 238±152 ml in controls (p=NS). After PCI, serum creatinine increased (>0.5 mg/dl) in 0% patients of CVVH-treated group and in 74% of saline group (p<0.0001) and, at discharge, in 5% and in 88%, respectively (p<0.0001). Temporary HD was required in 29% of cases of the saline group and in no case of the CVVH group. In 2 cases (saline group), permanent HD was required. In-hospital mortality was 2.4% in CVVH group and 14.7% in saline group (p<0.001).

Conclusions: In patients with chronic renal insufficiency undergoing PCI, periprocedural CVVH is an effective treatment to prevent renal function deterioration due to contrast nephrotoxicity and to improve in-hospital prognosis.

3372 Randomized comparison of tirofiban, eptifibatide, and abciximab in minimizing myocardial damage during high-risk percutaneous coronary intervention: TEAM pilot trial

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Background: The diverse results of various randomized PCI trials of GP IIb/IIIa inhibitors (GPI) may be due to different levels of platelet inhibiton (PI) achieved by a particular GPI agent. TEAM pilot trial is a double blind, randomized study of the three GPI during high-risk clinical (rest angina, post MI) or lesion (type C, ostial, calcified, thrombotic, multivessel intervention) PCI settings. TEAM study hypothesis was that with similar levels of PI (>90%), all three agents will have an equal class effect in reducing myocardial damage and 30-day major adverse cardiac events (MACE).

Methods: We analyzed 180 PCI patients randomized to one of the three arms: tirofiban (RESTORE dose), eptifibatide (PURSUIT dose), and abciximab (EPILOG dose), with similar baseline clinical, angiographic, and procedural characteristics. Patients with <90% PI (by RPFA with Ultegra device) after 10 min of GPI infusion, received additional half bolus of the blinded agent prior to PCI.

Results: In 232 lesions treated, angiographic success was 97.3% and procedural success 98.9%, 0.6/2.2% major/minor TIMI bleeding complications, 2.2/1.1% mild/severe thrombocytopenia in the entire group and were similar between the three agents. Mean peak activated clotting time was 255 sec and was similar between the three groups.

Results of the TEAM trial

Variable	Tirofiban (n=56)	Eptifibatide (n=61)	Abciximab (n=63)	p
Need for additional bolus (%)	58.9	31.1	53.9	0.004
Final PI prior to PCI (%)	93±4	93±3	93±4	NS
Any CKMB elevation (%)	16.1	14.7	14.3	NS
Troponin-I >2 ng/ml (%)	28.6	26.2	25.4	NS
30-day MACE (%)	5.4	3.3	4.8	NS

Conclusion: PCI patients with high-risk clinical/lesions require increased GPI dose compared to the recommended dose for an optimal PI. With this strategy, all three GPI had similar effect on myocardial salvage and 30-day MACE, and was not associated with increase in bleeding. Therefore, routine PI measurement may further improve the results of PCI in high-risk patients.

3373 Reduction in peri-procedural myocardial infarction by pre-procedural statin medication

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Background: Stenting-related myocardial injury has been recognized as a frequent and prognostically important event, depending in its extent at least in part upon microcirculatory impairment in association with platelet aggregation, inflammation, and increase in oxidative stress. Recent studies underscored the non-lipid-lowering effects of HMG-CoA reductase inhibitors (statins) with antithrombotic, anti-inflammatory, and anti-oxidative aspects. Thus, we tested the hypothesis that pre-procedural statin treatment is associated with a reduction in the extent of stenting-related myocardial injury without the need of lower serum lipid concentrations.

Methods: Series of 296 consecutive patients (pts.) undergoing stenting of a de-novo coronary or graft stenosis, stratified according to the pre-procedural status of statin therapy (229 statin-pos. pts.; 67 statin-neg. pts.). Incidence of peri-procedural myocardial injury was assessed by analysis of creatine kinase (CK; upper limit of normal (ULN) 70 IU/l for women, 80 IU/l for men), and cardiac troponin T (cTnT; rapid bedside test; threshold 0.1 ng/mL) before and 6, 12, and 24 hours after the intervention.

Results: Total cholesterol and LDL serum concentrations were not different between statin-pos. and statin-neg. pts. (209 ± 45 vs. 203 ± 43 and 137 ± 42 vs. 136 ± 41 mg/dL, p=NS). Compared with statin-neg. pts., the incidence of CK elevation >3x ULN was significantly lower in statin-pos. pts. (see table). Pre-procedural statin treatment was associated with a lower risk of post-procedural CK elevation >3x ULN in both univariate (RR 0.07, 95% CI 0.01-0.63; p=0.018) and multivariate analysis (OR 0.08, 95% CI 0.01-0.75; p=0.027).

Post-procedural cardiac marker outcome

	Statin-neg. (n=67)	Statin-pos. (n=229)	p value
pos. cTnT [%]	22.4	17.9	NS
CK 1-3x ULN [%]	14.9	14.4	NS
CK >3x ULN [%]	6.0	0.4	0.01

Conclusions: Pre-procedural statin treatment is associated with a reduction in the incidence of larger-sized, stenting-related myocardial infarctions. Prospective, randomized trials are warranted to further assess this cardioprotective effect of statins in coronary intervention.

EXPLOITING THE POTENTIALS OF CORONARY FLOW RESERVE

3374 Influence of adjunctive GP IIb-IIIa inhibitors or thrombus extraction devices on CFR in patients with acute coronary syndromes treated with stent

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Coronary distal embolization is a potential complication of patients with thrombus containing lesions treated by stents. Platelet aggregates or larger fragments of thrombus may produce transient alterations in coronary blood flow that could be minimized by mechanical or pharmacological methods. We studied the protective effect of thrombus aspiration devices (X-sizer® or Rescue®) versus glycoprotein IIb-IIIa inhibitors on the immediate and 24-hour coronary blood flow patterns after successful stent implantation. We included 45 patients with acute coronary syndrom due to thrombus containing lesions, 40 (88%), with a recent myocardial infarction. In 10 patients (group I) a mechanical aspiration of the thrombus was carried out before stent implantation, 24 patients (group II) received ReoPro® bolus and post-stent 12 hour infusion and the remaining 11 (group III) constituted the control group, with no adjunctive measures. After stent implantation, distal Doppler coronary flow velocity (APV) was measured in all patients at baseline conditions and post-adenosine intracoronary bolus. The same study was repeated 24 hours later. There were no differences among groups in terms of age, gender, clinical condition or lesion location. Immediate normalization of coronary flow reserve (CFR>2) took place in 1 patient from group I (10%), 1 from group II (4%) and 3 from group III(27%); p:ns. Serial changes of average peak velocities (cm/s) are shown in the table. Patients from group I had the highest CFR at 24 hours (p<0.05).

	Baseline APV	Hyperaemic APV	Post stent CFR	24 h baseline APV	24 h hyperaemic APV	24 h CFR
Group I	17.4 ± 9.4	28.1 ± 16.2	1.6 ± 0.3	18.5 ± 8.4	37.9 ± 11.3	2.2 ± 0.5
Group II	13.2 ± 8.5	18.2 ± 11.4	1.3 ± 0.3	15.8 ± 5.2	28.2 ± 9.9	1.8 ± 0.4
Group III	14.5 ± 5.7	23.1 ± 9	1.7 ± 0.3	17.7 ± 7	28.4 ± 10	1.7 ± 0.3

Conclusions: In patients with acute coronary syndromes successfully treated with stents, the immediate CFR is impaired despite the use of mechanical or pharmacological methods. An early (24 hours) recovery of mycrovascular function is observed in patients with adjunctive measures, specially in those with previous thrombus removal.

3375 Relationship between TIMI frame count and intracoronary Doppler measurements in patients treated with abciximab

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Background: The Thrombolysis in Myocardial Infarction frame count (TFC) is a reproducible, objective and quantitative index of coronary blood flow. Close linear correlation was observed between coronary velocities and TFC, but this relation was weaker after coronary angioplasty. Consequently, we sought to investigate whether abciximab may modify this correlation by inhibiting platelet activation in patients treated with elective coronary stenting.
Methods: The study cohort consisted of 12 patients (pts) who underwent elective stenting (PCI) of the left anterior descending coronary artery with abciximab (0.25 mg/kg IV bolus followed by 0.125 μg/kg/min infusion). Pts with myocardial infarction or general conditions known to impair distal microcirculation such as diabetes or left ventricular hypertrophy were excluded. Non ionic contrast injection was performed using an automatic injector (10 ml at 6 ml/sec) and cineangiography was recorded at 25 frames/sec. TFC analysis was done by two independent observers. Coronary velocities measurement were simultaneously obtained with a Doppler-tipped angioplasty wire positioned distally to the stenosis. Average peak velocity (APV) at baseline and following hyperaemia after 30 μg intra coronary adenosine were recorded three times, before angioplasty, after balloon and stenting, respectively. Aortic pressure, and heart rate were continuously recorded during the procedure.
Results: Minimal lumen diameter increased significantly from 1.20 ± 0.2 mm at baseline, to 1.80 ± 0.5 after balloon angioplasty and to 2.95 ± 0.4 mm after stenting. As anticipated, baseline APV were not significantly influenced by stent implantation, however APV during hyperaemia increased from 21 ± 10 to 43 ± 17 cm/sec after PCI (p < 0.001). Therefore coronary velocity reserve normalised in all of the cases (from 1.5 ± 0.4 to 2.5 ± 0.1 after PCI, respectively). Similarly, TFC was unchanged at baseline, and increased after stent implantation during hyperaemia (from 18 ± 4 to 8 ± 3 frames after PCI, p< 0.001). A significant linear correlation was found between APV and TFC measurements (r = 0.61, SEE = 15, p < 0.01) but with a notable scatter of the data. Neither mean aortic pressure nor heart rate were modified throughout the procedure.
Conclusion: During PCI with abciximab, TFC and Doppler flow measurements are grossly correlated. This study does not favour the hypothesis of a platelet dependent mechanism to explain these discrepancies and suggests that TFC cannot be used as a surrogate endpoint to assess coronary physiology.

3376 The ideal drug for no-reflow: comparison of adenosine, verapamil, nicardipine and nitroprusside

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Background: No-reflow phenomenon is a well described complication of emergency and elective percutaneous coronary angioplasty. Treatment of no-reflow with vasodilator drugs has been suggested. In search of the ideal drug, adenosine, verapamil, nicardipine and nitroprusside were compared relatively to their efficacy, lenght of action and potential side effects in normal pigs.
Methods: Intracoronary adenosine (10, 25, 50, 100, 150 and 300 mcg), verapamil (50, 100, 200 and 500 mcg), nicardipine (15, 50, 100 and 200 mcg) and nitroprusside (25, 50, 100, 250 and 500 mcg) were serially administered in a randomized, double-blinded fashion in the left circumflex coronary artery in 7 pigs. Coronary flow reserve was assessed using a continuous Doppler Flowire. Parameters including EKG, heart rate, pressure measurements (central venous, left ventricule, aortic and femoral), and LV dP/dT analysis were recorded.
Results: Optimal dosages for each drug in regard to the increase in CFR were respectively adenosine 300 mcg (2,93 ± 0,45), verapamil 200 mcg (2,16 ± 0,45), nicardipine 50 mcg (3,04 ± 0,43) and nitroprusside 250 mcg (2,97 ± 0,55). No significant difference was shown in CFR increase among adenosine, nicardipine and nitroprusside at optimal established dosage.However,verapamil was shown to be significantly less potent than these three drugs in terms of CFR increase (p = 0,01). Duration of effect was statistically different between all the drugs, with nicardipine presenting the most prolonged effect (1041 ± 157 sec, p < 0,01) compared with verapamil (328 ± 46 sec, p < 0,01), nitroprusside (87 ± 11 sec, p < 0,01) and adenosine (38 ± 12 sec, p < 0,01). Effect on systolic blood pressure was minimal with adenosine (-1,7 ± 0,9 mmHg), intermediate with verapamil (-6,0 ± 5,9 mmHg) and nicardipine (- 8,6 ± 7,2 mmHg), and pronounced with nitroprusside (-19,0 ± 5,7 mmHg). None of the drugs significantly affected heart rate at the optimal established dosage.
Conclusions: We conclude that there is equivalent CFR increase using adenosine, nicardipine or nitroprusside. These drugs are also clearly superior to verapamil to increase CFR. Nicardipine, when compared to adenosine and nitroprusside, offers equivalent potency and a much more prolonged vasodilator effect. Nitroprusside showed a clear tendancy to decrease systemic blood pressure but this side-effect was of short duration and auto-resolutive. Finally adenosine can safely be used at dosages higher than those accepted in actual clinical practice without significant side effects.

3377 Evaluation of microvascular reperfusion by ST segment resolution and coronary flow reserve after recanalized acute anterior myocardial infarction

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Background: Persistent ST segment elevation shortly after recanalization reflects sustained electrical transmural injury and correlates well with impaired myocardial reperfusion at the tissue level. Measurement of coronary flow reserve (CFR) is the physiological approach to assess the severity of coronary stenosis and microvascular dysfunction. We hypothesized that patients with a rapid ST segment return to baseline have a better microvascular function, as expressed by preserved CFR.
Methods: We studied 15 patients with a first anterior acute myocardial infarction, 12 treated with primary PTCA and 3 with intravenous thrombolysis. A surface ECG was obtained on admission and after recanalization (90 minutes after admission ECG). The sum of ST segment elevation was measured in V1 to V6 and I, aVL leads and the percentage of recovery of the summation at 90 minutes ECG was computed. Coronary blood flow velocity in the left anterior descending coronary artery was detected noninvasively 3±1 days after revascularization by transthoracic Doppler echocardiography. CFR was calculated by the ratio of the averaged peak systolic-diastolic flow velocity (APV) during adenosine infusion to baseline APV. A CFR >2.0 was regarded as normal.
Results: Eight out of the 15 patients (53%) had ST segment resolution (ST elevation <50% of initial value), while 7 did not, with the ST recovery percentage of 30±11% versus 74±19%, p< 0.001. CFR was 2.4±0.6 in patients with ST resolution, compared with 1.6±0.5 (p<0.01) in patients with persistent ST elevation. A normal CFR was present in 7 of the 8 (88%) patients with ST resolution, whereas only in 1 of the 7 (14%) with persistent ST elevation (p<0.05).
Conclusion: Assessment of microvascular reperfusion by ST segment resolution agrees with CFR measurement. ST segment resolution after revascularization indicates a better microvascular function, as demonstrated by preserved CFR.

3378 Influence of microvascular integrity on coronary flow reserve evaluated shortly after acute myocardial infarction

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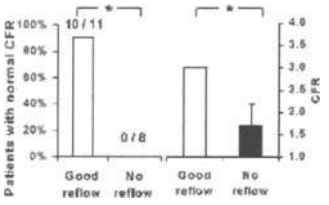
Background: Following acute myocardial infarction (AMI), the microcirculation can be damaged, with a reduction of coronary flow reserve (CFR) in the infarct related artery. We hypothesized that, in patients with AMI and no-reflow at myocardial contrast echocardiography (MCE), the CFR in the infarct related artery is reduced.
Methods: In 19 patients with anterior AMI submitted to primary PTCA and without residual stenosis we studied: 1) perfusion with MCE and harmonic power Doppler with intravenous Levovist and 2) coronary flow velocity in the left descending coronary artery with contrast-enhanced transthoracic echo Doppler at baseline and after adenosine injection. Patients had no-reflow if the ratio between the number of segments with perfusion defect and the total number of segments in the dyssynergic area was >0.5.
Results: Among the 19 patients with AMI, 11 showed a good reflow, while 8 showed the no-reflow phenomenon. The CFR was 3±0.6 in the 11 patients with a good reflow, and 1.7±0.5 ($p<0.0001$) in the 8 no-reflow patients. Ten of 11 (91%) patients with a good reflow at MCE, and none of the 8 (0%) patients with no-reflow (* $p<0.001$) showed a normal (>2.5) CFR. There was a significant negative correlation between the percentage extent of perfusion defect and the CFR ($p<0.0001$; $r=0.75$).



CFR after AMI.

Conclusion: In patients with AMI, CFR is more impaired in the presence of no-reflow at MCE. Contrast echocardiography allows a comprehensive noninvasive evaluation of both microvascular integrity and vasodilatory flow reserve after AMI.

3379 Can intracoronary Doppler flow wire predict viability detected by sestamibi SPECT after successful primary PTCA in patients with acute myocardial infarction?

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Background: The extent of myocardial salvage after primary percutaneous transluminal coronary angioplasty (PTCA) in acute myocardial infarction (AMI) is variable and can not be predicted on the basis of vessel patency. The aim of this study was to evaluate the tissue salvage and the microvascular integrity after successful intervention in AMI by coronary blood flow velocity and sestamibi perfusion imaging. Methods: Twenty-two patients (17m, 5 f; mean age 57±14 yrs.) undergoing primary PTCA and stent implantation for AMI were studied. 99mTC Sestamibi was injected intravenously before intervention and single photon emission computed tomography (SPECT) was performed immediately after successful reperfusion to determine the area at risk before PTCA due to the minimal 99mTC Sestamibi redistribution. Sestamibi SPECT was repeated 3 days and 6 months after AMI. Area at risk (%) was determined automatically by myocardial perfusion tomography (PERFIT) with the use of a multistage, 3D iterative inter-subject registration of patient images to normal templates (2SD) and myocardial salvage was calculated. Coronary flow velocity was measured using a Doppler-tipped guidewire in the infarct related artery after successful completion of primary PTCA and in an angiographically normal reference vessel. Absolute coronary flow reserve (CFR) and relative CFR (rCFR) were calculated using hyperemic to basal average peak velocity. Results: Despite successful reperfusion of the target vessel (TIMI grade III flow) CFR and rCFR remained impaired (1.8±0.9 and 0.77±0.21). Area at risk decreased significatly from 21±9% to 9±10% ($p<0.05$) corresponding to 11±8% myocardial salvage. Acute CFR and rCFR showed no correlation with the area at risk after primary PTCA. The increase of CFR within 6 months correlated with the myocardial salvage ($p<0.01$). Conclusions: Despite successful primary PTCA in AMI, CFR and rCFR remain often impaired because of a significant loss of microvascular integrity. The long-term success of primary PTCA can be assessed by myocardial salvage and the change of CFR which might be a useful parameter for additional reperfusion strategies such as glycoprotein IIb/IIIA receptor inhibition.

ELECTROCARDIOGRAM AND PROGNOSIS IN HEART FAILURE

3380 Reading electrocardiogram changes when an echo, a right heart catheterization, and a cardiopulmonary exercise test is available: are we wasting our time?

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Background: Previous studies demonstrated that intraventricular conduction delays predict poor prognosis in congestive heart failure (CHF). However, little is known about the prognostic implications of QRS widening in such patients. Methods: We analyzed 105 CHF patients referred for heart transplantation (age 53±10 years; 88% male; 40% ischemic cardiomyopathy; LVEF 24±6%, 56% in NYHA class III-IV) undergoing a concomitant complete clinical and instrumental (i.e. electrocardiogram (ECG), echocardiogram, right heart catheterization, cardiopulmonary exercise test) assessment (index evaluation). Inclusion criteria was the availability of a previous ECG performed > 6 months before index evaluation. Results. At two years from index evaluation, incidence of cardiac death or need for heart transplantation (CD/HT) was overall 61±6%. At multivariate analysis, QRS widening occurred before index evaluation turned out to be a predictor of CD/HT (adjusted RR per msec of increase [95% CI] 1.02[1.01-1.04], P=0.003) independently from age, NYHA class, EF, systolic blood pressure, mean pulmonary artery pressure, and peak oxygen consumption. Incidence of CD/HT in patients with QRS widening >=0.5 msec/month (a cut-off corresponding to the mean value of QRS widening) at two years was higher as compared to those with QRS widening <0.5 msec/month (76±7 vs. 49±8%, $P<0.001$). Conclusions. Accelerated QRS widening detected by surface ECG is independently and unfavorably associated with an adverse outcome in CHF. Prospective studies are needed to investigate the usefulness of this parameter for selecting candidates to HT and for evaluating the effects of biventricular pacing.

3381 Clinical characteristics and survival of patients with chronic heart failure and prolonged QRS duration

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Background: Prolongation of QRS duration (>120 ms) is a common finding in patients with chronic heart failure (CHF), being associated with an impaired prognosis. Whilst resynchronisation of ventricular contraction may be of benefit in patients with severe QRS prolongation (>150 ms), this has yet to be determined for patients with moderate QRS prolongation (120-150 ms).
Methods: We evaluated 155 patients with CHF of varying severity (New York Heart Association, NYHA class 2.6±0.8, mean±SD) secondary to left ventricular systolic impairment. Maximal exercise testing was performed in 149 patients from which peak oxygen consumption (VO2) was determined. The mean follow-up of the 155 patients was 838±748 days (range 4 to 2531), of which 62 died or underwent heart transplantation after 4 to 2160 days (mean 482±514). Patients were sub-grouped into 3 categories according to QRS duration: <120 ms (normal QRS, n=82), 120 to 150 ms (moderate prolongation, n=44) and >150 ms (severe prolongation, n=29).
Results: When compared to patients with a normal QRS duration, those with moderate prolongation had a significantly worse NYHA class (2.4 vs 3.0), peak VO2 (17.7 vs 14.9 mL/kg/min) and left ventricular ejection fraction (26 vs 22%, respectively, all $p<0.05$). In contrast, patients with moderate QRS prolongation had similar impairment of NYHA class and peak VO2 as compared to those with severe QRS prolongation (all $p>0.05$). The optimal QRS duration for predicting 2 year event free survival in the CHF patients was 120 ms (receiver operating characteristic analysis: area under curve 0.73; 95% CI 0.64 to 0.81). Patients with a QRS duration >120ms had a worse prognosis at 2 years (cumulative event free survival 47%; 95% CI 35 to 59) as compared to those with a normal QRS duration (84%; 95% CI 75 to 93; $p<0.0001$).
Conclusions: CHF patients with moderate QRS prolongation share similar impairment of exercise capacity and functional class to those with severe prolongation. A QRS duration of 120 ms is the best medium-term predictor of event free survival. Whether biventricular pacing would benefit patients with moderate QRS prolongation is not known and requires further evaluation in prospective clinical trials.

3382 Left but not right bundle branch block is an independent predictor of prognosis in patients with heart failure: report from the IN-CHF Registry

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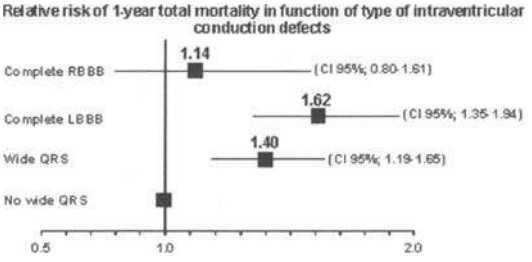
Introduction: Many clinical factors influence the prognosis of heart failure (HF). While left bundle branch block (LBBB) has been already identified as a negative prognostic factor, the independent effect of right bundle-branch block (RBBB) is still unknown. The aim of the study was to compare the effects of these two different intraventricular conduction defects on prognosis of HF.

Methods and Results: These data were derived from the database of the Italian Network on Congestive Heart Failure (IN-CHF). Entry in the Registry required that patients had a diagnosis of HF based on the ESC guidelines. We analyzed 1- year follow-up data of 5517 unselected outpatients with HF of different etiologies. Wide QRS was defined when QRS duration was >120msec in a 12-lead ECG. Wide QRS was present in 2066 patients (37.4%), 25.2% with complete LBBB, 6.1% with complete RBBB, 6.2% with other intraventricular defects. When we considered 1-year mortality at univariate analysis patients with complete LBBB had a significant higher mortality than those without LBBB (16.10% vs 11.95%, p=0.0001) but this was not true for complete RBBB (11.90% vs 11.95%, p= NS). At univariate analysis, using the patients with no wide QRS as reference group, the relative risk of death of patients with wide QRS and complete LBBB was statistically higher (Figure). When we adjusted for clinical and hemodynamic parameters only complete LBBB still remained an independent predictor of death in patients with HF (RR 1.36 CI 95% 1.15-1.61).



Conclusions: LBBB but not RBBB is an independent predictor of prognosis in outpatients with HF.

3383 Univariate analysis of frequency domain HRV indices as predictors of mortality in chronic heart failure; 5-year results of the UK heart study

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Background: CHF is associated with progressive autonomic dysfunction. This alteration is believed to have a direct role in the process of deteriorating cardiac function and by implication may be related to the timing of cardiac death. Markers of cardiac autonomic activity have therefore been investigated for their potential use as prognostic indicators providing the possibility for identifying high-risk individuals, who may benefit from more intensive therapy.

Methods: The baseline heart rate variability (HRV) of 529 CHF patients, aged 18-80 years, NYHA grade I-III was studied using 24 hour ambulatory ECG recordings. Time domain HRV indices (standard deviation of normal RR intervals(SDNN), number of increases in successive RR intervals >50ms(sNN50), root of the mean of square of successive RR intervals (rMSSD) and frequency domain HRV indices (total power (TP), very low power (VLF), low power (LF), and high power (HF)) were evaluated and related to total mortality, sudden cardiac death, and progressive cardiac death at five year follow up using univariate analysis and Cox proportional hazard model. Baseline assessment of cardiac function, biochemistry and cardiac rhythm were obtained in all patients.

Results:

	All Cause mortality	Progressive Cardiac	Sudden Cardiac
	OR, P Value	OR, P Value	OR, P Value
SDNN	0.886, 0.0001	0.863, 0.0002	0.947, 0.146
sNN50	0.994, 0.217	0.982, 0.056	1.003, 0.651
RMSSD	0.957, 0.641	0.963, 0.779	1.062, 0.636
TP	0.942, 0.006	0.881, 0.001	1.006, 0.807
HF	0.853, 0.020	0.698, 0.01	0.985, 0.850
LF	0.780, 0.006	0.671, 0.01	0.965, 0.743
VLF	0.934, 0.016	0.846, 0.002	1.016, 0.635
**NLF	1.448, 0.001	1.531, 0.002	1.202, 0.211
**NHF	0.738, 0.005	0.688, 0.008	0.856, 0.313

OR: Odds Ratio, ** Normalised Values

Conclusions: A lower SDNN index was significantly associated with higher all cause mortality and progressive cardiac death. All the frequency domain indices whether quoted in absolute or normalised values were significantly associated with all cause and progressive cardiac death.

3384 QT dispersion in hypertensive diabetic and non-diabetic patients with congestive heart failure

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Background: Blood pressure (BP) and QT dispersion (QTd) are important prognostic risk factors in congestive heart failure (CHF) patients (pts).

Aim: QTd in hypertensive diabetic (D) and non-diabetic (ND) pts with CHF and its relation to ambulatory BP measurement values in D pts was analysed.

Patients and methods: Group D: 70 pts (m/f: 40/30, mean age 64.7±9.0 y), group ND: 52 pts (m/f: 28/24, 62.5±10.9 y). Diagnosis of CHF was proved clinically (ECG, ECHO: EF<40%). D was defined clinically or by positive oGTT. Hypertension (HT; mmHg) was mild - moderate (150.9/87.4 - D, 146.6/89.8 - ND) and of 5.5 y (D) and 6.2 y (ND) duration. Mean BMI was 27.7±3.1 kg/m^2 (D), 28.2±5.8 kg/m^2 (ND). Serum lipids were normal or borderline (HDL-C, TG). Smokers (23% D, 25% ND). NYHA class: I (4.3% D, 9.6% ND), II (51.4% D, 57.7% ND), III (41.4% D, 30.8% ND, p<0.05), IV (2.9% D, 1.9% ND). Treatments: ACEI (92.0% D, 95.0% ND), diuretics (86.0% D, 83.0% ND), digoxin (67.0% D, 54.0% ND, p<0.05), beta-blockers (41.0% D, 44.2% ND). QTd and rate corrected QTd (Bazett, QTdc) were defined as the difference between the max and min QT and QTc intervals, resp. Statistical analysis: Chi-square test, Student's t-test. Significant differences for p<0.05.

Results: Both groups matched (sex, age, duration & intensity of HT & obesity, serum lipids, smoking, NYHA class, treatment). The QT and QTc intervals, QTd and QTdc in D and ND pts are in table. D pts with QTdc>65 ms in comparison to QTdc<65 ms had significantly higher BP (133±14/80±11 vs. 112±14/65±6 mmHg, resp.) and significantly higher BP night/day ratio (0.94±0.05/0.89±0.07 vs. 0.86±0.06/0.80±0.05, resp.).

QT interval characteristics

Parameters [ms]	Group ND (n=52)	Group D (n=70)	p
QT interval max	401.7 ± 18.6	409.2 ± 20.3	= 0.074
QT interval min	341.2 ± 19.0	344.8 ± 17.9	> 0.35
QTc interval max	421.1 ± 15.8	429.7 ± 14.3	= 0.008
QTc interval min	372.0 ± 19.4	387.5 ± 21.0	< 0.001
QTd	47.1 ± 17.8	61.2 ± 19.6	< 0.001
QTdc	51.0 ± 13.3	65.0 ± 21.8	< 0.001

Conclusion: HT D pts with CHF have higher QTd than HT ND pts. D pts have higher BP values during the night in the group with higher QTd (> 65ms) in comparison with D pts with lower QTd.

3385 Age, cardiac revascularization procedures and heart rate variability: influence on short- and long-term prognosis after cardiac rehabilitation

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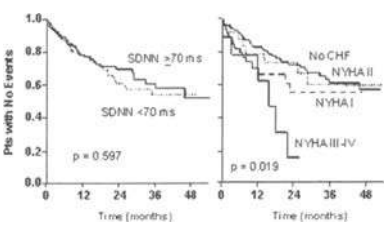
Heart rate variability (HRV) is a useful tool to assess prognosis in patients (pts) with acute myocardial infarction (AMI) or congestive heart failure (CHF). With this study we wanted to evaluate the relationship among age, cardiac revascularization procedures and HRV, comparing CABG (n=123, 69+9 yrs) and PTCA (n=96, 63+12 yrs) pts consecutively enrolled in a programme of cardiac rehabilitation with Controls (n=90, 57+15 yrs). Time domain analysis of HRV was obtained through 24-hours ECG Holter recordings. CABG and PTCA pts had significantly lower values of HRV when compared to Controls (SDNN – CABG: 70 ± 24 vs PTCA: 92 ±35 vs Controls: 141±23 ms, p=0.001; RMSSD – CABG: 22±10 vs PTCA: 27±10 vs Controls: 35±13 ms, p=0.001). Age was also inversely related to HRV parameters. These relationships were maintained after adjustments for history of angina, CHF, diabetes, hypertension and MI. During the follow-up, mortality and new admissions to hospital were associated only with the presence and the degree of CHF, while no relationship was identified between HRV and prognosis, as usually observed in pts with myocardial infarction or left ventricular failure not undergoing CABG or PTCA (Kaplan-Meier and Cox Models).

In conclusion, age and cardiac revascularization procedures exert a deep influence on HRV, independently increasing the loss of homeostatic capacities, and creating important substrates allowing the development of frequent arrhythmias such as atrial fibrillation.



NEW MARKERS OF HEART FAILURE

3386 Dynamics of the left ventricular mass in heart failure patients with and without cachexia: a prospective cardiovascular magnetic resonance study

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Background: Although the "cachectic heart" has been described as a pathologic decrease in the size and mass of the heart, no studies have followed in-vivo changes in cardiac dimensions or left ventricular (LV) mass over time in chronic heart failure (CHF) patients with cardiac cachexia. This study sought to assess the direction and magnitude of changes in LV mass and cavity size over time in patients with CHF body wasting, *i.e.* cardiac cachexia.
Methods: Repeated cardiac magnetic resonance (CMR) studies were performed in 9 CHF patients with cardiac cachexia compared to 28 matched CHF patients without cachexia (age 69±12 versus 65±9 years, p=0.20; body mass index 23±1 versus 29±5 kg/m^2, p=0.0005). LV mass and volumes were analyzed blind to patient classification twice, at baseline and after a mean follow-up of 15 (range 7-22 months). According to our previous findings, CMR requires 9 patients with heart failure to detect a 10 g change in LV mass over time with a statistical power of 90% and an alpha-error of 0.05.
Results: At baseline, LV end-diastolic volume (197±78 versus 203±65 ml) and end-systolic volume (131±75 versus 126±63 ml), LV mass (213±44 versus 222±62 g), and LV ejection fraction (38±19% versus 40±16%) did not differ between patients with and without cachexia (all p>0.10). During follow-up, there was a significant decrease in LV mass in patients with cachexia (-16 g, p<0.05) and a trend to increase in LV mass in patients without cachexia (+7 g, p=0.12, comparison between groups: p=0.010).
Conclusions: The direction of changes over time in LV mass differs in CHF patients with cachexia as compared to those without cachexia. A significant decrease in LV mass occurs in patients with cardiac cachexia. This study documents in vivo the occurrence of wasting of the left ventricle in patients with chronic heart failure who demonstrate general body wasting.

3387 Low T3 syndrome: a strong predictor of death in patients with heart disease

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Background: Low-T3 syndrome has been documented in patients with several heart disease and commonly interpreted as an 'euthyroid sick syndrome', i.e. an adaptive compensatory response to conserve energy. However, some clinical and experimental data have suggested a potential negative impact of low T3 state on the prognosis of cardiac patients. Aim of the study. To assess the role of thyroid hormones in the prognosis of a large population of patients with heart disease.
Methods: 573 consecutive patients with known heart disease (78% with documented ischemic heart disease or primary left ventricular dysfunction) underwent prospectively thyroid function profile evaluation. Patients were divided in two subgroups as follows: Group I, 173 (30%) patients with low T3, i.e. with fT3 below the lower limit of the reference interval (fT3< 2.0 pg/ml); Group II, 400 patients with normal fT3 (* 2.0 pg/ml). Events considered were cumulative deaths and cardia death. Results. During the 1-year follow-up, there were 25 cumulative deaths in group I and 12 in group II (14.4% vs 3%, p<.0001) of which 13 cardiac deaths in group I and 6 in group II (7.5% vs 1.5%, p<.0006) respectively. Using the Cox proportional hazards model, fT3 was the most important predictor of cumulative death (hazard ratio 3.582, p<.0001), followed by age (hazard ratio 1.051, p<.004), ejection fraction (hazard ratio 1.037, p<.006) and dyslipidemia (hazard ratio 2.955, p<.002). With interactive procedure, fT3 added higher significant prediction of death after considering all the other traditional variables (c2 18.10, p<.001). Conclusion. Low-T3 state is a strong predictor of death in cardiac patients. In these patients with low-T3 levels the administration of substitutive doses of synthetic T3 can be hypothesized in the attempt to improve prognosis.

3388 Vascular oxidative stress and endothelial dysfunction in patients with chronic heart failure: role of xanthine oxidase and superoxide dismutase

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Background: Endothelial vasomotor dysfunction contributes to increased peripheral vascular resistance and reduced myocardial perfusion in chronic heart failure (CHF). Impairment of endothelium-dependent vasodilation in patients with CHF is, at least in part, due to accelerated degradation of nitric oxide by oxygen radicals. We therefore determined activities of endothelium-bound extracellular superoxide dismutase (ecSOD), a major vascular antioxidant enzyme system, and endothelium-bound xanthine oxidase (XO), a radical forming enzyme within the arterial wall, and their relation to flow-dependent, endothelium-mediated vasodilation (FDD) in patients with CHF.
Methods and Results: ecSOD and XO activities, released from the endothelium into plasma by heparin bolus injection (5000 IE), were studied in fourteen patients with CHF (NYHA III; dilated cardiomyopathy) and ten age-matched control subjects. ecSOD activity was analyzed using a spectrophotometric assay, whereas xanthine oxidase activity was determined by electron spin resonance spectroscopy (ESR) using the spin label C-PH. FDD of the radial artery was measured using high-resolution ultrasound and was assessed before and after intra-arterial infusion of the antioxidant vitamin C (25 mg/min.) to determine the portion of FDD inhibited by radicals.
In patients with CHF endothelium-bound ecSOD activity was substantially reduced (5.0 ± 0.7 vs. 14.4 ± 2.6 U x ml-1 x min-1; P < 0.01) and closely related to FDD (r=0.61). Endothelium-bound XO activity was increased by more than 200% (38 ± 10 vs. 12 ± 4 nmol O2.- x μl-1; P < 0.05) and inversely related to FDD (r=-0.35) in patients with CHF. In patients with low ecSOD and high XO activity a substantially greater benefit from the antioxidant vitamin C on FDD was observed, i.e. the portion of FDD inhibited by oxygen radicals correlated negatively with ecSOD (r=-0.71), but positively with XO (r=0.75) activity.
Conclusion: These results suggest that both, reduced ecSOD and increased XO activity contribute to increased vascular oxidant stress in patients with CHF. This loss of "vascular oxidative balance" within the arterial wall likely represents a novel mechanism contributing to endothelial dysfunction in patients with CHF.

3389 Reduced levels of the GLUT4 transport protein in skeletal muscle relate to impaired insulin sensitivity in chronic heart failure

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Background: Chronic heart failure (CHF) is an insulin resistance state, independently of an ischaemic aetiology. The underlying patho-mechanism is not known.
We aimed to investigate, a) whether the expression of GLUT4, the main insulin dependent glucose transport protein is reduced in skeletal muscle in CHF compared to healthy controls, and b) whether expression of GLUT4 is correlated with insulin resistance in CHF patients.
Methods: In 29 patients with CHF (age 66±2y, NYHA I/II/III/IV: 2/16/10/1, peak VO2 20.0±1.5 ml/kg/min) and in 7 healthy control subjects (age 58±5y) a skeletal muscle biopsy was obtained from the gastrocnemius muscle or quadriceps muscle (fine needle technique). Total amount of GLUT4 protein was assessed by western blotting (results normalised to the myosin heavy chain band of a coomassie blue stained gel). In 20 patients and 3 controls insulin sensitivity was assessed (by intravenous glucose tolerance testing using a minimal modelling approach). Body composition was analysed by dual energy x-ray absorptiometry (DEXA) scanning.
Results: Patients and controls were similar for BMI (25.5±0.8 vs 25.8±1.5 kg/m^2) and total and regional fat mass (all p>0.2). GLUT4 was lower in CHF patients than in controls (0.75±0.07 vs 1.24±0.19 arbitrary units, p<0.01). Reduced GLUT4 occurred in parallel to severity of CHF, being lowest in NYHA III/IV (0.596±0.08 p<0.01 vs controls) compared to NYHA I/II (0.84±0.09, p<0.05 vs controls). GLUT4 was lowest in patients with ischaemic aetiology (0.69±0.06, p<0.01 vs to controls) compared to those with dilated cardiomyopathy (1.01±0.2). Insulin sensitivity was 1.71±0.3 min-1.μU.ml-1.104 in CHF patients compared to 3.57±0.6 min-1.μU.ml-1.104 in controls (p<0.05). In patients and controls, the amount of GLUT4 correlated directly with insulin sensitivity (r=0.55) and inversely with fasting insulin levels (r=-0.52, both p<0.01).
Conclusion: In CHF, total amount of GLUT4 transport protein in skeletal muscle tissue is reduced compared to healthy controls. This may contribute to the insulin resistance seen in CHF patients.

3390 Elevated plasma amylase levels are corellated with circulating interleukin-6 activation in advanced chronic heart failure

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Background: It has been reported that proinflammatory cytokine activation is associated with mesenteric venous congestion in advanced chronic heart failure (CHF) This study investigates whether plasma amylase is elevated in severe CHF and whether this elevation is correlated with proinflammatory cytokine activity in the plasma of CHF patients.
Methods: Plasma levels of amylase, tumor necrosis factor-a (TNF-a) and interleukin-6 (IL-6) were measured (ELISA,Cytoscreen US-Biosource International) in 37 patients with severe CHF (NYHA III: 18, NYHA IV: 19; Ischemic: 25, Dilated: 12; LVEF: 28±4%) and 20 healthy control subjects.
Results: Plasma levels of amylase (392±29 vs 170±13 mg/dl, $p<0.005$), TNF-a (6.5±1.9 vs 2.7±0.7 pg/ml, $p<0.001$) and IL-6 (7.3±1.7 vs 3.2±0.5 pg/ml, $p<0.001$) were significantly elevated in CHF patients as compared with those of healthy control sublects. NYHA IV patients exhibited significantly higher levels of plasma amylase, TNF-a and IL-6 than those of NYHA III patients (all $p<0.05$).There were no significant differences in plasma amylase and proinflammatory cytokines between patients with ischemic CHF and those with dilated cardiomyopathy. In CHF patients plasma amylase levels were significantly correlated with plasma IL-6 activity ($r=0.48$, $p<0.05$) and right atrial pressure ($r=0.57$, $p<0.01$). Finally, plasma IL-6 was correlated with right atrial pressure ($r=0.55$, $p<0.03$).
Conclusions: I) Plasma amylase levels are elevated in CHF patients according to the severity of the disease. II) Plasma amylase levels are correlated with IL-6 activation, possibly as a result of mesenteric venous congestion in severe CHF.

3391 Endotoxin sensitivity and immune competence in chronic heart failure

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Background: Raised concentrations of endotoxin (lipopolysaccharide/LPS) are found in patients with chronic heart failure (CHF). Tolerance of monocytes to LPS can be induced by LPS itself resulting in a downregulation of cytokine response to LPS challenge. This phenomenon of LPS desensitization has also been suggested for CHF. We investigated whether CHF patients really show a desensitization to LPS stimuli at rest or after physical exercise, which was used as a model of limited inflammatory reaction.
Methods and Results: We prospectively studied 35 patients with CHF (60 ± 10 years, 9 women) and 20 healthy control subjects with cardiopulmonary exercise testing. At rest and directly after exercise blood samples were taken for the quantitative determination of HLA-DR expression of monocytes as a measure for immune competence and for the measurement of TNFa generation after ex vivo stimulation by LPS. Left ventricular ejection fraction (26 ± 6% vs. 60 ± 3%, $p < 0.001$) and peak oxygen uptake (15.0 ± 3.6 vs. 19.8 ± 4.1 ml/min/kg, $p < 0.001$) were significantly lower in CHF patients compared to controls. HLA-DR expression was comparable in CHF patients and controls at rest (24103 ± 8323 vs. 25784 ± 7734 ABS/cell, n.s.) as well as after exercise (27154 ± 9820 vs. 29452 ± 8677 ABS/cell, n.s.). TNFa production by LPS stimulated monocytes ex vivo was higher in CHF patients compared to controls at rest (445 ± 293 vs. 315 ± 141 pg/ml, $p < 0.05$) and after exercise (523 ± 396 vs. 395 ± 183 pg/ml, n.s.).
Conclusions: TNFa generation capacity is higher at rest and equal after physical exercise in CHF patients compared to controls. Thus patients with CHF seem to show a marked susceptibility to low inflammatory stimuli and no desensitization to LPS. This phenomenon could explain higher concentrations of inflammatory cytokines, susceptibility to infections, cytokine induced catabolic metabolism, and increased mortality in CHF.

NEUROHORMONAL MECHANISMS IN HEART FAILURE: CURRENT PERSPECTIVES

3392 Parathyroid hormone-related protein is produced in the myocardium and increased in patients with congestive heart failure

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Background and Objectives: Parathyroid hormone-related protein (PTHrP) is produced in a wide variety of different cells including cardiomyocytes. Its production is augmented by mechanical and neurohumoral stimulation, and PTHrP has positive chronotropic and vasodilatory effects. Thus, in the heart, PTHrP has the potential to serve as a new mechano-sensitive regulatory molecule. In this study, we evaluated peripheral and central levels of PTHrP in patients with congestive heart failure (CHF), and test the hypothesis that PTHrP is released from the heart in patients with CHF.
Methods: Intact full-length PTHrP (i-PTHrP) and C-terminal PTHrP (c-PTHrP) levels were measured in the plasma of 64 patients with CHF and 12 controls. Plasma PTHrP concentrations in the coronary sinus and aortic root were also measured in 18 CHF patients and 10 controls.
Results: Both plasma i-PTHrP and c-PTHrP levels were significantly higher in patients with CHF (0.31 ± 0.03 pmol/L and 37.5 ± 1.3 pmol/L, respectively) than in normal control subjects (0.24 ± 0.04 pmol/L and 29.7 ± 1.5 pmol/L, respectively). Both PTHrP measurements increased according to NYHA class ($p<0.05$), with those in NYHA III showing levels of i-PTHrP and c-PTHrP that were 77.5% and 50.5% higher than controls. There were significant correlations between c-PTHrP levels and plasma norepinephrine, BNP, angiotensin II, endothelin-1 levels ($R = 0.32, 0.21, 0.21$ and 0.33, respectively, $p<0.05$). Plasma i-PTHrP was significantly correlated with left ventricular ejection fraction (LVEF), end-diastolic and end-systolic dimensions ($p<0.05$). Plasma i-PTHrP levels were significantly higher in the coronary sinus than in the aortic root in CHF patients, but among controls concentrations of i-PTHrP were indistinguishable at these two sites. There were no significant relationships between plasma c-PTHrP level of the coronary sinus and pulmonary capillary wedge pressure (PCWP), cardiac index (CI), stroke volume index (SVI), left ventricular end-diastolic pressure (LVEDP), left ventricular end-diastolic volume (LVEDV) or LVEF. On the other hand, plasma i-PTHrP level of the coronary sinus was significantly correlated with LVEDV ($R = 0.61$, $p<0.05$) but it was not correlated with PCWP, CI, SVI, LVEDP or LVEF.
Conclusions: This is the first report demonstrating that PTHrP is produced in the myocardium and increased in CHF; and suggests that PTHrPs measurements might be useful in clinical assessment of these patients.

3393 Blunted baroreflex control of renal sympathetic activity in patients with heart failure

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Heart failure is associated with a blunted heart rate and vascular baroreflex response. Hitherto, studies on renal sympathetic function in terms of renal baroreflex mechanisms are sparse in patients with heart failure (CHF).
The aim of this study was to examine whether selective unloading of cardiopulmonary and sinoaortic baroreceptors failed to reflexely increase renal sympathetic activity in patients with CHF compared with healthy subjects.
Methods: Patients, n=11, age 51±3 y(mean±SE), with CHF, LVEF 19±2%, NYHA II-III and healthy subjects (HS), n=5, age 55±2 y, underwent a right heart and renal vein catheterization. Hemodynamics, renal and total body noradrenaline (NA) spillover rates and plasma renin renal gradient (PRA-gradient) were measured at baseline and during a continuous infusion of glyceryl trinitrate (GTN). NA-spillover was assessed by radioisotope dilution technique and renal blood flow was measured by infusionsclearance of PAH. After baseline measurements, all subjects received GTN until cardiac filling pressures were reduced without affecting arterial pressures (non-hypotensive level). GTN infusion rate was then increased until a stable reduction of mean arterial pressure by 10 mmHg was achieved (hypotensive level).
Results: In HS, no differences in NA spillover rates were found at the non-hypotensive level, whereas the PRA-gradient increased ($P<0.05$). During hypotension in renal NA spillover tended to increase, without any statistically significant changes in total body NA spillover (renal NA spillover: baseline 527±173, non-hypotensive 686±173, hypotensive 824±129 pmol/min, P=NS.; PRA-gradient: baseline 0.097±0.07, non-hypotensive 0.30±0.08*, hypotensive 0.30±0.05* Ang I x mL-1 x h-1, *$p<0.05$ vs. baseline). In CHF, the non-hypotensive level resulted in a small increase in renal NA spillover. At the hypotensive level, renal NA spillover was reduced (baseline 1377±159, non-hypotensive 1511±173, hypotensive 982±208*# pmol/min, $P<0.05$ vs. baseline* and vs. non-hypotensive#), whereas the PRA-gradient increased (baseline 2.9±0.97, non-hypotensive 4.0±1.3, hypotensive 15.4±6.4* Ang I x mL-1 x h-1, *$P<0.05$ vs. baseline). Total body NA spillover rates remained unchanged (baseline 5065±1005, non-hypotensive 4852±948, hypotensive 4753±737 pmol/min, P=NS.).
Conclusions: These results indicate a defective baroreflex control of sympathetic outflow to the kidney in human CHF with a paradoxical decrease of the latter when sinoaortic baroreceptors are unloaded. PRA increased in both groups, suggesting a dominating influence of intrarenal factors on renin release.

3394 Modulation of the positive inotropic effect of angiotensin II by the endocardial endothelium and endothelin-1

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Introduction: Recent studies have suggested that the vascular effects of angiotensin II (angt II) are partially dependent on the production and release of endothelin-1. These neurohumoral agents also have important myocardial actions, but their acute interaction at this level has not yet been explored. The main goal of our study was to investigate the modulation of angt II positive inotropic effect by the endocardial endothelium (EE) and by endothelin-1 (ET-1). **Methods:** The effects of the addition of increasing concentrations of angt II (10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}) were evaluated in rabbit right papillary muscles (modified Krebs; 0.6 Hz; 1.8mM Ca^{2+}; 35°C) in the following conditions: (i) intact EE (Protocol A; n=11); (ii) after the selective removal of EE with Triton X-100 (0,5%; 1s; Protocol B; n=8) (iii) intact endothelium in the presence of PD-145065 (Protocol C; n=9; 1 mM), a nonselective antagonist of ET-1 receptors. Calculated parameters: active tension (AT; mN/mm^2), peak rates of tension rise and decline (dT/dtmax and dT/dtmin, respectively; $mN/mm^2/s$), time to half relaxation (tHR, ms), peak shortening (PS; mm) and peak rate of shortening (dL/dtmax; mm/s). Results are presented as mean±SEM in % of baseline ($p<0.05$). **Results:** In Protocol A, angt II had a dose-dependent positive inotropic effect, maximal for 10-6 M. At this concentration, angt II increased 122±13% AT, 117±16% dT/dtmax, 86±9% dT/dtmin, 12±2% tHR, 121±18% PS and 101±17% dL/dtmax. In Protocols B and C the maximal effect was significantly decreased. In Protocol B, angt II 10-6 M increased 72±16% AT, 32±7% dT/dtmax, 59±11% dT/dtmin, 95±24% PS and 41±22% dL/dtmax, without altering tHR. In Protocol C, the same concentration of angt II increased 48±11% AT, 54±14% dT/dtmax, 39±8% dT/dtmin and 40±10% EM, without altering tHR and dL/dtmax. The positive inotropic effect of angt II was not statistically different between Protocols B and C. **Conclusions:** The positive inotropic effect of angt II was significantly attenuated by the selective removal of EE and by the nonselective endothelin receptor antagonist, confirming the initial hypothesis of a potential interaction between these agents in myocardial function. These results have particular importance for the pathophysiology of heart failure, where both neurohumoral agents are activated and the endothelium is dysfunctional.

3395 Increased serum levels of metalloproteinases and their tissue inhibitors in patients with heart failure and cardiac cachexia

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Introduction: Extracellular matrix (ECM) plays an important role in left ventricular remodeling. The structure of ECM is maintained by the dynamic equilibrium of metalloproteinases (MMP), which degrade ECM, and of their tissue inhibitors (TIMP). Neurohormones and cytokines regulate MMP and TIMP actions. Their role in CHF has not been studied. The purpose of this study was to examine the role of MMP and TIMP in patients with CHF, with and without cardiac cachexia, a condition that is associated with neurohormonal activation and increased mortality.
Methods: We studied 30 men with CHF, NYHA II-IV, of whom 20 had cachexia, aged 66±9 (mean±SD), and Left Ventricular ejection fraction (EF) 28±8%. We measured serum levels of metalloproteinase-1 (MMP-1), metalloproteinase-3 (MMP-3) and tissue inhibitor of metalloproteinases-1 (TIMP-1). Cachexia was defined as the loss of >7.5% of body weight, in a 6-month period, which was not caused by diet or edema absorption.
Results: MMP-1 and MMP-3 were significantly increased in patients with cardiac cachexia compared to those without cachexia (30±40 vs 11±8 and 231±170 vs 130±100 ng/ml, $p<0.05$ respectively). Levels of TIMP-1 were relatively increased in patients with CHF and cardiac cachexia (360±170 vs 251±150 ng/ml, $p<0.08$).
Conclusion: In this study it is shown that in patients with CHF and cardiac cachexia there is intense activation of MMP-1 and MMP-3 and to a lesser degree activation of TIMP-1. The disturbance of MMP/TIMP equilibrium is a possible mechanism of Left Ventricular remodeling and may serve as marker of adverse prognosis in patients with cardiac cachexia.

3396 Temporal changes of plasma soluble apoptosis mediators are associated with heart failure neurohormonal overactivation and clinical deterioration

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Background: Recent investigations indicate that an abnormal immune response and apoptotic process contribute to adverse left ventricular (LV) myocardial remodeling in chronic heart failure (CHF). This study investigates whether alterations in soluble apoptosis mediators (sTNFRI: soluble Tumor Necrosis Factor Receptor I, sFas: soluble Fas, sFasL: soluble Fas Ligand) occur in relation to plasma neurohormonal activation and progress of the syndrome in patients with CHF.
Methods: Plasma levels of sTNFRI, sFas and sFasL were serially examined in 25 CHF patients (age: 65±5 yrs; ischemic: 16, dilated: 9) at baseline and up to 6 months using commercially available ELISA tests (Biosurce International; Diaclone). Plasma norepinephrine (PN) and plasma renin activity (PRA) were quantified by HPLC and RIA, respectively. Finally, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD) and diastolic transmitral flow [early (E) and atrial (A) filling velocities, E/A ratio, deceleration time (DT) of E] were echocardiographically determined.
Results: When compared to age- and sex-matched healthy controls (n=15), sTNFRI (4.2±0.9 vs 1.8±0.1 ng/ml, $p<0.01$), sFas (4.8±1.1 vs 2.5±0.7 ng/ml $p<0.05$) and sFasL (41.3±7.7 vs 16.5±3.1 pg/ml, $p<0.001$) plasma levels at baseline were significantly elevated in CHF patients. During follow up, an absolute increase in plasma sTNFRI from baseline (+1.2±0.3 ng/ml, $p<0.01$) was accompanied by increase in PN ($p<0.05$) and PRA ($p<0.05$), worsening functional class ($p=0.057$) and sorter DT of E ($p<0.05$) in CHF patients. An absolute increase in plasma sFas during follow up (+1.5±0.5 ng/ml, $p<0.05$), was also associated with an elevation in PN ($p=0.060$), worsening functional status ($p<0.05$) and increased LVEDD ($p<0.01$). Finally, an increase in plasma sFasL from baseline (+16.1±3.9 pg/ml, $p<0.01$) was associated with worsening functional status ($p=0.051$). There were no significant differences in temporal changes of plasma soluble apoptosis mediators and neurohormones between CHF patients with ischemic and those with dilated cardiomyopathy.
Conclusions: I) Soluble apoptosis mediators are elevated in CHF patients. II) Temporal changes in neurohormonal system activation may influence the expression of soluble apoptosis mediators despite the etiology of CHF. III) These changes in apoptotic process and neurohormonal activation may be associated with the progression of LV remodeling and subsequent clinical deterioration in CHF.

3397 Interdependence of atrial and ventricular neuronal function

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To characterize the interdependency of function displayed among atrial (RAGP) and ventricular (VIGP) neurons, their response characteristics to alterations in the ventricular mechanical or chemical milieu and the coordination of atrial and ventricular neuronal activities were evaluated in 10 anesthetized dogs. This was done during basal states, during enhanced ventricular sensory inputs, during altered cardiodynamics and during focal ventricular ischemia. Atrial and ventricular neuronal activity displayed periodic coupled behavior (cross correlation coefficients of activities that reached 0.88±0.03; range 0.71-1) for 15-30 seconds periods of time during basal states. Periods of coupled activity occurred every 30-50 seconds. Atrial and ventricular neurons were activated when their ventricular sensory inputs were exposed to angiotensin II (VIGP: 16.6±4.5 basal vs. 30.1±7.4, $P<0,01$) (RAGP: 17.7±4.0 basal vs 53.0±16.1, p=n.s), the alpha-2-adrenoceptor agonist clonidine or the nitric oxide donor SNAP (VIGP: 16.0±2.3 basal vs. 21.4±4.1, $P<0,01$) (RAGP: 7.4±1.7 basal vs 20.3±2.5, p=n.s). Most atrial neurons were activated by ventricular mechanosensory inputs (VIGP: 20.2±4.9 basal vs. 15.6±4.8, $P<0,01$) (RAGP: 11.7±3.6 basal vs 22.0±5.5, p=n.s), while most ventricular ones responded to atrial mechanosensory stimuli (VIGP: 9.5±3.0 basal vs. 21.8±5.4, $P<0,01$)(RAGP 14.9±3.1 basal vs. 15.5±4.3, p=n.s.). Fewer neurons responding to epicardial application of adenosine, bradykinin, an alpha-1- or beta-1-adrenoceptor agonist or veratridine. Both populations of neurons were excited when right atrial neurons were exposed to nicotine (VIGP: 14.4±3.0 basal vs. 28.2±9.0, $P<0,01$) (RAGP: 8.6±1.5 basal vs 18.3±6.4, p=n.s). Transient ventricular ischemia activated atrial and ventricular neurons both before, but not after their decentralization (VIGP: 16.5±4.2 before vs. 11.2±2.7 after decentralisation, $P<0,01$) (RAGP: 17.7±3.1 before vs 9.4±4.0 after decentralisation, p=n.s). These data indicate that atrial and ventricular neurons receive multimodal ventricular sensory inputs, particularly with respect to angiotensin II, alpha-adrenoceptor agonists and nitric oxide donors. Furthermore, both populations of neurons frequently respond to perturbations in the mechanical or chemical milieu of the heart similarly. It is concluded that interdependence of function is displayed by atrial and ventricular neurons, forming the basis for coordinate control over regional cardiac function in physiological and ischemic states.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND A2 BLOCKERS: ROLES IN HEART FAILURE THERAPY

3398 Valsartan reduces morbidity in heart failure patients receiving background angiotensin-converting enzyme inhibitors but not receiving beta-blockers: results from Val-HeFT

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Background: The Valsartan Heart Failure Trial (Val-HeFT) demonstrated that the angiotensin II receptor blocker valsartan reduced overall morbidity in heart failure (HF) patients when added to standard background therapies e.g. ACE inhibitors (ACEi) and/or beta blockers. However, many HF patients are unable to tolerate, have contraindications to, or are not prescribed beta blockers. Accordingly, we sought to examine the effect of valsartan on morbidity and mortality amongst Val-HeFT patients receiving an ACEi in the absence of beta blockers.
Methods: Val-HeFT was a placebo-controlled study of valsartan 160 mg bid in 5010 NYHA class II-IV HF patients. The study's co-primary endpoints were time to death & time to first morbid event (death, sudden death with resuscitation, intravenous inotropic or vasodilator therapy for >= 4 hours or hospitalisation for HF). The present analysis examined the effect of valsartan on these endpoints in the 3034 Val-HeFT patients who were receiving an ACEi, but not a beta blocker, at randomisation.
Results: The baseline characteristics of this subgroup did not differ from the overall Val-HeFT population. At study end (mean duration 23.0 months), mortality did not differ significantly between placebo (22.5%) and valsartan (21.8%). In contrast, the incidence of morbid events was significantly lower with valsartan (31.0%) than placebo (36.3%), hazard ratio 0.817, p= 0.002. This was due mainly to a 34% reduction in risk of first hospitalisations for HF (224 in valsartan, 316 in placebo; p<0.00001). Significant improvements in left ventricular ejection fraction, quality of life and neurohormonal parameters were also observed with valsartan versus placebo (all P=<0.001).
Conclusion: Valsartan significantly reduces morbidity in HF patients when added to ACEi therapy in the absence of beta blockers. These benefits most likely arise as a result of more complete blockade of the renin-angiotensin system.

3399 Comparative and combined antiremodelling effects of angiotensin-converting enzyme inhibitors and beta-adrenoceptor blockers in congestive heart failure

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Background: Because left ventricular (LV) remodeling determines prognosis in congestive heart failure (CHF) the attenuation of this process is an important therapeutic goal.
The aim of our study was to assess the relative long-term effects of angiotensin converting enzyme inhibition or beta-blocker (BB) therapy and their combination on LV remodeling process in patients (pts) with CHF.
Methods: 106 consecutive pts (mean age 58.8±0.8, male 84) with NYHA III functional class CHF caused by ischemic or idiopathic dilated cardiomyopathy were randomly assigned to receive: Perindopril (P) (up to 4 mg/day, n=23), Carvedilol (C) (up to 25 mg twice a day, n=20), Bisoprolol (B) (up to 10 mg/day, n=19) alone and combined therapy of P+C (n=24) and P+B (n=20) at same doses in addition to diuretics and digoxin. Echocardiography was performed to assess LV end-diastolic (EDV), end-systolic (ESV) volumes, LV mass, sphericity index (SI), relative wall thickness (RWT) and pulmonary capillary wedge pressure (PCWP) at baseline and 12 months in all pts.
Results: BB monotherapy produced significant reduction in ESV (at 7%, p<0.05 in C and 9.7%, p<0.05 in B), leading to a greater median increase in EF compared with P (5.84% vs. 1.95%, p<0.05 and 5.9% vs. 1.95%, p<0.05). Monotherapy and combined treatment of each drug caused similar significant reduction in PCWP (p<0.05) and EDD (p<0.05). Adjunctive treatment produced a trend toward a greater increase in EF from baseline (at 5.1%, p=NS in P; 5.8%, p<0.05 in C; 6.0%, p<0.05 in B; 9.6%, p<0.05 in P+C and 10.1%, p<0.05 in P+B) and significantly greater favorable changes from baseline levels in LV mass (at 7.5%, p<0.05 in P; 8.1%, p<0.05 in C; 7.2%, p<0.05 in B; 15.1%, p<0.01 in P+C and 14.3%, p<0.01 in P+B), SI (at 7.9%, p<0.05 in P; 8.1%, p<0.05 in C; 7.7%, p<0.05 in B; 15.4%, p<0.01 in P+C and 15.5%, p<0.01 in P+B) and RWT (at 7.7%, p<0.05 in P; 8.2%, p<0.05 in C; 7.4%, p<0.05 in B; 15.3%, p<0.01 in P+C and 14.9%, p<0.01 in P+B).
Conclusions: Although long-term P therapy did not alter LV ESV, and either C or B associated with reduction in chamber volume, each drug produced favorable changes in LV mass, SI and RWT. The combined treatment resulted in further improvement in the attenuation of LV remodeling process.

3400 Pulse pressure responses in patients treated with valsartan and hydrochlorothiazide combination therapy

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Background: Pulse pressure (PP), which is defined as the systolic blood pressure (BP) minus the diastolic BP, is believed to be a powerful indicator of cardiovascular risk. However, there is little information from clinical trials concerning drug-induced changes in PP. This parameter was examined in a comparative study of the angiotensin receptor blocker (ARB) valsartan and hydrochlorothiazide (HCTZ) as a combination therapy for hypertension in patients not controlled on valsartan monotherapy.
Aims: The effect of valsartan monotherapy (Val-mono) and two doses of valsartan plus HCTZ were compared in patients with mild to moderate HT whose BP was not adequately controlled with Val-mono.
Methods: This multicentre double-blind, parallel-group study employed a 4-week single-blind run-in period on Val 160mg o.d. to select patients whose BP was inadequately controlled with monotherapy. At the end of this period (baseline) 2002 patients were randomised to either same treatment Val-mono (663 patients) or one of 2 combination therapies, Val 160mg plus HCTZ 12.5mg o.d. (Val/HCTZ12.5) or Val 160mg plus HCTZ 25mg o.d. (Val/HCTZ25) – (663 and 657 patients respectively). Patients were treated for 8 weeks and evaluations performed every 4 weeks. The primary variable was a change from baseline in the Mean Sitting Diastolic BP (MSDBP) and a change in the Mean Sitting Systolic BP (MSSBP).
Results: The mean sitting PP before the Val-mono run-in was 58.9 mmHg (SD 11.8) in patients, who were later randomized to Val-mono, 59.1 mmHg (SD 11.8) in those randomized to Val/HCTZ12.5 and 58.9 mmHg (SD 11.6) in those randomized to Val/HCTZ25. After the Val-mono run-in period, PP had decreased in all groups to 54.1 mmHg (SD 12.2), 54.7 mmHg (SD 12.1) and 54.1 mmHg (SD 12.03), respectively. A mean decrease of 4.66mm overall. After the 8 week double-blind period, additional reductions in PP were observed with combination therapies to 52.4 (SD 12.4) mmHg for Val/HCTZ12.5 and 51.2 (SD 12.1) mmHg for Val/HCTZ25. Giving overall reductions of 6.7mm and 7.7mm, respectively.
Conclusions: In this trial with selected hypertensive patients whose BP was not adequately controlled with valsartan monotherapy there was an initial improvement in PP with Val-mono. Uptitration to Val/HCTZ produced further PP reductions suggesting that this therapeutic combination is highly effective in reducing PP.

3401 Suppression of renal aquaporin-2 overexpression by valsartan and fosinopril as a new treatment target of congestive heart failure

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Background: In patients with congestive heart failure (CHF), fluid overload is the main clinical manifestation though their mechanism is not fully understood. Recently, a family of proteins, the aquaporins, has been shown to regulate water reabsorption in different regions of the kidney which is likely to play a role in water retention in CHF. Treatment with angiotensin converting enzyme inhibitor or angiotesin II type-1 receptor blocker have been shown beneficial in patients with CHF. However, their effect on water balance and aquaporins expression remains unclear. This study investigated the role of these drugs on renal aquaporins expression in a rat model of CHF secondary to myocardial infarction.
Method: CHF was induced by left anterior descending coronary artery ligation in 8-week old Sprague Dawley rats. They were randomized to receive fosinopril (Fos), valsartan (Val) or combination of both drugs (Co) for 4 weeks. The mRNA expression of aquaporin-1 and -2 in kidneys was quantified by multiplex reverse transcription-polymerase chain reaction using TATA Box protein gene as a control. The protein expression of aquaporin was estimated by Western blot hybridisation and immunohistochemistry. Blood pressure was measured by non-invasive tail-cuff technique.
Results: The blood pressure was significantly reduced in all the treatment arms, without change in heart rate. Aquaporin-2 mRNA expression was increased significantly after AMI in both cortical (Sham: 18±4 vs CHF: 35±6 vs Fos: 25±11 vs Val: 23±6 vs Co: 26±9%; $p<0.01$ for Sham vs CHF, $p<0.05$ for CHF vs any treatment group) and medullary tubules (Sham: 23±2 vs 51±8 vs 20±5 vs 23±5 vs 24±8%; $p<0.005$ for Sham vs CHF, $p<=0.001$ for CHF vs any treatment group), and was normalized after any of the 3 medical regimens. Aquaporin-2 protein expression was significantly increased in CHF, and was attenuated by drug treatment (Sham: 0.86±0.25, CHF: 1.54±0.37, Fos: 1.16±0.32, Val: 1.16±0.19, Co: 1.37±0.10, ANOVA $p<0.05$). Immunohistochemistry showed that the sites of expression of aquaporin-2 are the renal tubules, especially from the medullary collecting ducts. On the other hand, aquaporin-1 mRNA and protein expressions were unchanged in CHF or after medical treatment.
Conclusion: Treatment with either Fos, Val or Co could modify the increased renal expression of aquaporin-2 in CHF secondary to AMI. As aquaporin-2 has a role in enhancing water reabsorption, suppression of this regulatory protein may contribute to the alleviation of fluid overload and CHF rehospitalisation in the clinical setting.

3402 Effect of valsartan on beta-adrenergic receptor kinase (betaARK1) activity in heart failure

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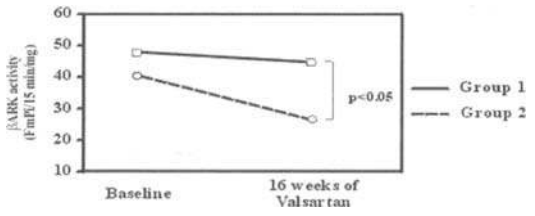
In chronic heart failure the increased beta-adrenergic receptor kinase (betaARK1) activity causes downregulation of beta-adrenergic receptors, thus favouring heart failure progression. Little is known about the interaction between renin-angiotensin system and betaARK1 activity. To better understand this relationship we evaluated the effect of an AT1 receptor antagonist (ARB) on betaARK1 activity.
We studied 24 patients (mean age 59 ± 9, 18 males) with NYHA functional class II or III (mean value: 2.3±0.5), left ventricular ejection fraction <40% (mean value: 29.7±6.5), who were not taking ACE-inhibitors, ARBs and beta-blockers from at least 1 month before the study. Patients were in stable clinical conditions and received the maximum tolerated dose of Valsartan (V) once daily (up to 160 mg). At baseline and after 16 weeks of V administration, angiotensin II (ATII) plasma levels and betaARK1 activity were evaluated.
V was not not able to significantly increase ATII plasma levels (from 12.6±6.8 pg/ml to 17.1±16.8 pg/ml) and reduce betaARK1 activity (from 44.8±28.4 FmPi/15 min/mg to 37.9±22.2 FmPi/15 min/mg). However, patients showing an increase of ATII plasma levels (group 1) after V had significantly lower values of betaARK1 activity than those found in patients in whom ATII did not increase (group 2) (ANCOVA analysis) (figure). V dosage was not different between the two groups (153±24 mg vs 154±22 mg).



In conclusion, in chronic heart failure, Valsartan is able to reduce betaARK1 activity only when ATII is increased. This favourable effect may be due to the ATII interaction with AT2 receptors when the AT1 receptors are blocked.

3403 Comparative influence of angiotensin-converting enzyme inhibitors, beta-blockers and nitrates on left ventricular diastolic filling in congestive heart failure

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Background: Recent studies have shown, that left ventricular (LV) diastolic filling is a strong predictor of survival in chronic heart failure (CHF). A direct comparison of the diastolic effects of angiotensin converting enzyme inhibitors, b-blockers and long-acting nitrates has rarely been performed.
The aim of our study was to assess the relative long-term effects of Fozinopril (F), Carvedilol (C) and Isosorbide Dinitrate (ID) on Doppler-derived parameters of diastolic filling in CHF.
Methods: 80 consecutive patients (pts) (mean age 58.9±0.2 years, male 66) with NYHA III-IV functional class CHF of ischemic origin were randomly assigned to treatment with F (up to 20 mg/day) for 6 months, followed by 6 months of combined treatment F+C (up to 25 mg twice daily, n=42) and F+ID (up to 60 mg/day, n=38) in addition to diuretics and digoxin. Peak early (E) and late (A) transmitral filling velocities, E/A ratio, acceleration (AT) and deceleration times (DT) of E-wave, LV isovolumic relaxation (IVRT), overall LV filling time (OFT) were obtained using pulsed-wave Doppler echocardiography at baseline, 6 and 12 months. All pts were in sinus rhythm and had the restrictive filling pattern (E/A>2, DT<130 msec).
Results: F treatment has significantly prolonged AT (from 75±1.8 to 81±2.4 msec, $p<0.05$) and DT (114±8.1 to 138±8.6 msec, $p<0.05$), decreased E (87.3±2.1 to 80.4±2.8 cm/sec, $p<0.05$) and E/A (2.31±0.14 to 1.9±0.15, $p<0.05$) and had trend toward increasing of IVRT (42±4.2 to 50.4±6.1 msec, p=NS), OFT (352±11 to 380±14 msec, p=NS) and A (37.8±3.6 to 42.3±1.1 cm/sec, p=NS). Adding C has resulted to further prolongation of AT (to 88±2.6, $p<0.05$) and DT (to 170±12.6, $p<0.05$), increasing of E (to 70.2±4.0, $p<0.05$) and E/A (to 1.4±0.2, $p<0.05$) and has significantly prolonged IVRT ((to 70.2±7.6, $p<0.05$) and OFT (to 410±5.1, $p<0.05$), leading to improved late diastolic filling, depicted by increased A (to 50.1±0.8, $p<0.05$). Treatment with ID has significantly prolonged IVRT (to 72.2±5.4, $p<0.001$) and OFT (to 411±12, $p<0.02$), increased A (to 52.2±2.2, $p<0.05$), decreased E (to 67.9±5.6, $p<0.05$) and E/A (to 1.3±0.25, $p<0.05$) and had tendency to further prolongation of AT (to 85±3.7, p=NS) and DT (to 155.4±7.7, p=NS).
Conclusions: All tested drugs have significantly improved LV diastolic filling, but affected different parameters and thus apparently acted through different mechanisms. Therefore the combined therapy may result in additive favorable changes in LV diastolic function.

CONDUCTION DISTURBANCE AND VENTRICULAR FUNCTION

3416 Is QRS duration a good index of right to left ventricular systolic asynchrony? Comparison with conventional and tissue Doppler imaging criteria

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Background: Biventricular pacing is a new promising technique aimed to achieving cardiac resynchronisation through inter- and intraventricular delay correction in heart failure. Therefore, accurate diagnosis of desynchronisation of right (RV) and left (LV) ventricular activation is of crucial importance. The usual accepted selection criteria for biventricular pacing include NYHA III-IV, LV dilatation, LV EF < 35% and QRS duration > 150 ms.
Aim: To assess right to left ventricular asynchrony by comparing QRS duration, right- (RV) and left ventricular (LV) pre-ejection delay measured by conventional Doppler and tissue Doppler imaging (TDI).
Methods: 50 patients (Pts) with primary dilated cardiomyopathy (NYHA III, LVEF<40%, LVEDD>60mm) were divided into 3 groups according to QRS duration (ms): Gr 1 (n=28, QRS<110), Gr 2 (n=13, 110<QRS<150) and Gr 3 (n=19, QRS>150). Echo parameters of RV to LV asynchrony were blindly measured by: 1) the difference between the onset of QRS and the onset of aortic and pulmonary flow, respectively (QAo-QPulm,ms); 2)the difference between the onset of QRS and the peak of systolic velocities recorded at the lateral corner of tricuspid and mitral annulus,respectively (QM-QT, ms).
Results: RV to LV asynchrony assessed by QAo-QPulm>40 was present in: 9/28Pts (32%) in Gr1; 3/13 (23%) in Gr2 and 14/19 (74%) in Gr3. In Pts with QAo-QPulm>40, QM-QT was significantly higher in all groups than in Pts with QAo-QPulm<40: Gr 1: 90±35 vs 34±18 ms; Gr2: 96±44 vs 44±22 ms and Gr 3: 107±35 vs 27±21 ms, $p<0.05$. QM-QT<80ms identified 31/34 Pts with QAo-QPulm<40 while QM-QT>80 identified 15/26 Pts with QAo-QPulm>40. No significant correlation was found between QRS duration and QAo-QPulm and QM-QT values, respectively. At the opposite, QM-QT values were significantly correlated with QAo-QPulm ($r=0.78$, $p<0.01$).
Conclusion: Accurate diagnosis of RV to LV asynchrony should not be only based on QRS duration but should combine mechanical indices derived from conventional and tissue Doppler imaging in order to better identify the potential patients to benefit from resynchronisation therapy.

3417 Timing of regional myocardial motion and deformation in cardiomyopathies with LBBB: a Doppler myocardial and strain rate imaging study

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Cardiac resynchronisation therapy (CRT) aims to improve regional myocardial asynchrony and haemodynamic function in pts with heart failure and left bundle-branch block (LBBB). Exact timing of regional function might be important for selecting patients and optimal pacing site. Doppler Myocardial Imaging(DMI) quantifies regional myocardial velocities and has been proposed for guiding CRT. However besides myocardial deformation, velocities are reflecting overall cardiac motion. Regional deformation rate(Strain Rate) and deformation(Strain, S)(calculated from regional velocity gradients)are less influenced by cardiac motion. This study investigated the timing of regional mechanical activation in ischemic(ICM) and idiopathic dilated cardiomyopathies(DCM) with LBBB and normals(nls) measured by DMI and Strain Rate Imaging (SRI).
Methods: Colour DMI data was obtained at >150 frames/s from the left ventricular(LV) sept, lat, inf, ant and post walls (apical window, longitudinal function) in 10 pts with DCM and LBBB(age 52±14y, QRS 169±29ms, EF 22±8%), 10 pts with ICM and LBBB(age 64±11y, QRS 155±26ms, EF 30±8%) and 10 nls(age 51±15y, QRS 79±12ms, EF 69±11%). Data was post processed to determine time from onset of QRS to maximal systolic or post systolic myocardial velocity(Vm) and deformation(Sm). LV walls with earliest and latest maximal motion/deformation were selected in each patient. Analysis was performed with custom made software enabling exact timing of global cardiac events.
Results: Earliest and latest Vm and Sm were variable within each patient or normal. Earliest Vm occurred in the sept wall in 50% of nls(150±21ms), in 20% of DCM (216±49ms) and in 40% of ICM (176±36ms) while 60% of nls (239±50ms), 50% of DCM (347±63ms) and 40% of ICM (292±40ms) had latest maximal motion in the post wall. Earliest Vm was found in the ant wall in 40% of DCM and in 30% of ICM. Earliest Sm occurred in the sept wall in 40% of nls (356±36ms), in 70% of DCM (385±67ms) and in 60% of ICM (372±55ms) while 60% of nls (488±56ms), 50% of DCM (593±58ms) and 50% of ICM (560±68ms) had latest maximal deformation in the post wall. Of all investigated subjects, 10% had earliest and latest Vm and Sm in the same walls.
Conclusions: Location of earliest and latest mechanical activation in DCM and ICM with LBBB and nls was highly variable throughout the LV walls. Earliest/latest maximal velocity compared with earliest/latest deformation within one patient occurred most often in different cardiac walls. Selecting patients and guiding CRT only on base of maximal velocities might have its limitations.

3418 Quantitative tissue Doppler can measure and localize improvement of ventricular dyssynchrony in dilated cardiomyopathy after biventricular pacing

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Background: Dilated cardiomyopathy (DCM) is characterized by abnormal left ventricular (LV) activation and contraction, that can be coordinated by biventricular (BIV) pacing, resulting in improved LV ejection fraction (EF). The aim of this study was to provide new indexes of LV contractile synchronicity obtained by quantitative Tissue Doppler Echocardiography (TDE) and to use them to evaluate the effect of BIV pacing on contractile dyssynchrony in patients with DCM.
Methods: Thirteen patients with DCM, NYHA class III-IV and QRS duration > 120 msec underwent a TDE study before and within 24h after BIV pacemaker implantation using a GE Vivid-Five echo scanner. Color high frame rate TDE cineloops were analyzed in the 4-chamber view extracting velocity profiles at a segmental level. The time intervals between the beginning of systolic shortening at basal septum and lateral wall (septum-lateral wall synchronicity index, SL-SI, msec), at basal and apical septum (intra-septal synchronicity index, IS-SI, msec), and at basal and apical lateral wall (intra-lateral synchronicity index, IL-SI, msec) were measured. The LV-EF was measured by the monoplane Simpson's rule.
Results: After BIV pacemaker implantation, SL-SI decreased from 122.0±48.0 to 53.1±47.1 msec ($p=0.0007$), IS-SI decreased from 74.8±47.1 to 37.1±31.6 msec ($p=0.0278$), and IL-SI decreased from 45.1±34.5 to 25.7±25.4 msec ($p=0.0229$). EF increased from 22.8±5.4 to 30.9±4.9% ($p=0.0001$) and QRS duration decreased from 196.0±27.0 to 157.0±19.0 msec ($p=0.0007$). SL-SI, IS-SI and IL-SI correlated inversely and significantly with EF ($r=-0.56$, $p=0.0029$; $r=-0.50$, $p=0.01$; $r=-0.47$, $p=0.0156$, respectively).
Conclusions: TDE allows direct measurement of intraventricular synchronicity, providing new indexes that also localize the level of dyssynchrony. In patients with DCM, this technique shows that the improvement in intraventricular synchronicity after BIV pacing occurs both within and between the LV walls and correlates with acute improvement in LV-EF. TDE, therefore, can potentially be helpful to guide ventricular resynchronization therapy in heart failure.

3419 Tissue Doppler imaging assessment of asynchrony predicts positive left ventricular remodelling after biventricular pacing in heart failure

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Resynchronization by biventricular pacing (BP) has been shown to reverse left ventricular (LV) remodeling in patients with heart failure (HF). Nevertheless, the prediction of benefit remains controversial. Tissue Doppler imaging (TDI) allows precise assessment of regional electromechanical coupling time (EMCT).
Aim: To determine a value of conventional- and TDI-derived echocardiographic parameters to predict benefit of the BP on LV remodeling.
Methods: Twenty-one consecutive patients with HF (NYHA 3.2±0.8) and wide QRS complex (179±28 ms) undergoing BP were studied prospectively by echocardiography. LV morphology and conventional Doppler derived indices of LV filling and ejection were assessed prior to BP. In addition, differences between regional EMCT in basal segments of the LV (LV asynchrony, LVasyn) and in basal left and right ventricular free wall (interventricular asynchrony, LV-RVasyn), respectively, were assessed by TDI. At 3 months follow-up, responders (R) were defined by an absolute increase in LV ejection fraction (LVEF) > 5% (n=15).
Results: LVEF increased significantly in R (22±5 vs 33±7%, p<0.01) but not in nonresponders (NR) (21±4 vs. 22±4%, NS). Baseline heart rate, QRS duration and PQ interval, LV dimensions and EF were similar in both groups (not shown). LV filling time (LVFT) was shorter (38±15 vs. 48±17% of cardiac cycle, p<0.05) and isovolumic contraction (IVCT) longer (20±7 vs. 14±11% of cardiac cycle, p<0.05) in R vs. NR. LVasyn (73±18 vs. 47±11 ms, p<0.05) and LV-RVasyn (82±24 vs. 48±13 ms, p<0.05) were greater in R vs NR, respectively. The accuracy of TDI-derived indices to predict an increase in LVEF was superior to conventional echo-Doppler indices (table).

	Sensitivity	Specificity	PPV	NPV	Accuracy
LVFT < 45%	67	67	83	44	67
IVCT > 15%	73	67	85	50	71
LVasyn > 65 ms	80	83	92	63	81
LV-RVasyn > 55 ms	80	83	92	63	81
LVasyn > 65 or LV-RVasyn > 55 ms	93	83	93	83	90

Conclusions: The TDI-derived parameters of asynchrony appears to be accurate predictors of the positive effects of BP on the LV remodeling. The use of such-derived indices may help to avoid unnecessary implantations.

3420 Ischaemic and not ischaemic myocardial post-systolic motion in patients with left bundle branch block: analysis of pulsed tissue Doppler

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Aim of the study: Pulsed Tissue Doppler (PW-TD) assessment of posterior interventricular septum (IVS) asynchrony in patients (pts) with left bundle branch block (LBBB) and with and without left anterior descending coronary artery (LAD) stenosis.
Population and methods: 42 consecutive pts (males: 21; mean age = 59±11 years) with chronic, complete LBBB underwent coronary angiography, standard Doppler-echo and PW-TD, placing the sample volume at the level of posterior septum and of the mitral annulus, in apical 4-chamber view. Myocardial systolic indexes (systolic peak velocity = Sm, pre-contraction time = PCTm and contraction time = CTm), diastolic measurements (early diastolic and atrial velocities - Em and Am, Em/Am ratio, relaxation time = RTm) and post systolic motion (PSM) peak velocity were obtained. Pts were divided into 2 groups according to the absence (group A, 27 pts) or presence (group B, 15 pts) of LAD stenosis >50%.
Results: see table. In the overall population PSM was related to age (r = -0.38, p<0,01), septal wall thickness (r = -0.38, p<0.01) and ejection fraction (EF) (r =0.32, p<0.05). By multivariate analysis EF (B=0.32) and significant LAD stenosis (B=0.43; both p<0.05) were independent predictors of PSM (cumulative R square = 0.24, p<0.05) while sex, age and diastolic blood pressure did not enter the model.

	Group A	Group B	P
Sm (cm/s)	6.17 (1.8)	5.19 (0.8)	<0.05
PCTm (ms)	133.1 (35.5)	143.5 (33.5)	<0.05
CTm (ms)	242 (58.1)	240.6 (55.3)	NS
Em (cm/s)	6.7 (1.6)	7.0 (1.9)	NS
Am (cm/s)	7.7 (3.8)	9.9 (3.7)	<0.05
Em/Am	0.83 (0.5)	0.76 (0.2)	NS
RTm (ms)	133.8 (37.2)	159.3 (27.5)	<0.02
PSM (cm/s)	5.3 (1.8)	8.0 (4.0)	<0.005

Conclusions: PW-TD allows to distinguish different patterns of septal myocardial asynchrony in LBBB with and without coronary artery disease. Pts with ischemic LBBB are characterized by a greater amplitude of PSM and longer length of PTCm and, above all, of RTm. LAD stenosis and EF are to be the main determinants of PSM magnitude.

3421 Doppler tissue imaging and congenital long QT syndrome

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Our objective was to evaluate the value of Doppler Tissue Imaging (DTI) in patients with long QT syndrome (LQTS) as a new phenotypic marker.
Methods: Ten patients with congenital LQTS (mean age; 34 ± 9 years) and 14 control subjects were studied. Standard echocardiography and DTI analysis were performed. Using an offline computer, myocardial velocities were measured in basal and mid segments of the septal, lateral, posterior and anterior walls, in apical view. Peak velocities and time intervals were measured in each segment.
Results: Conventionnal echocardiography was normal for both groups. DTI analysis demonstrated increased systolic and diastolic peak velocities for all segments in LQTS patients. In LQTS patients, increase was significant in almost segments, by example in basal septal (Peak S: 7.2 vs 4.6 cm/s; Peak E: -10 vs -6.9 cm/s; p < 0.05) and mid septal walls(Peak S: 4.7 vs 3.2 cm/s; Peak E: -9.3 vs -5.5 cm/s; p < 0.05). Regional isovolumic relaxation time and systolic velocity half time (VHT) were significantly longer in LQTS group with a prolonged late systolic phase, resulting in a plateau morphology.
These preliminary results show an increase in systolic and diastolic peak velocities, with an increase in the regional isovolumic relaxation time in patients with LQTS. DTI seems to be an interesting new phenotypic marker for LQTS.

INNOVATING APPLICATIONS OF TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

3422 Eustachian valve is a confounder of contrast echocardiography but not of color Doppler in detecting a right-to-left-shunt across a PFO

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Patent foramen ovale (PFO) is an accepted risk factor for paradoxical embolisation. Transesophageal contrast echocardiography (cTEE) is accepted as the method of choice for the diagnosis of PFO, but its diagnostic accuracy compared with color Doppler and with an associated Eustachian valve (EV) has not been established. The eustachian valve is a remnant of the embryonic right valve of the sinus venosus, which directs the blood from the inferior vena cava to the interatrial septum and across the PFO (if present). It is seen in the majority of newborn infants but much less frequently in adults, studied by transthoracic echocardiography
The aim of this study was to determine the influence of a large Eustachian valve on the accuracy of contrast and color Doppler echocardiography in detecting a right-to-left-shunt across a PFO.
Methods: In 292 consecutive patients (age 42±12 years) with cryptogenic stroke we asertained the precence of PFO and EV using TEE. None of these patients had a right or left heart pathology. A PFO was diagnosed based on the observation of right-to-left passage of contrast bubbles or by using color Doppler with a low Nyquist limit (20-45 cm/sec) if turbulent right-to-left flow through the valve-like structure could be documented. In case of conflicting results contrast agent was administered via a femoral vein cTEE-IVC. A large EV was defined with a size >1.5 cm measured in the bicaval view.
Results: A total of 192 pts (66%)showed evidence of a PFO with either echo technique. A PFO could be detected in 166 of 204 pts (56.8%) by cTEE [specifity 100%], versus 184 of 204 pts (64%) by color Doppler [specifity 97%]. A large EV was measured in 31 pts with PFO vs in 6 pts without PFO (p<0.001). The presence of a large EV decreased the sensitivity of cTEE from 81% (without EV) to 61% (p<0.001), whereas color Doppler sensitivity was unchanged 90%
Conclusion: The presence of a large EV decreases the accuracy of cTEEin detecting PFO, whereas color Doppler is not confounded by EV. EV confounds the clinical value of cTEE but not of color Doppler TEE in detecting PFO.

3423 Do left-sided echo contrast agents improve diagnostic accuracy of transoesophageal echocardiography in patients with suspected aortic dissection?

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Transesophageal echocardiography (TEE) has a high sensitivity and specificity to diagnose a suspected aortic dissection (AD) by interpretating 2D, M-Mode, and colour doppler information. Contrast echocardiography (CE) is widely used for assessment of left ventricular wall motion in patients (pat.) with poor image qualities. At present it is not known if CE gives further information in pat. with suspected AD.

Methods: TEE with CE was performed in 43 consecutive pat. (31 m; 12 f; mean age 65+14 y) with unexplained thoracic pain and suspected AD (clinical, CT, TEE). 12 pat. had a prior cardiovascular operation (aortic valve replacement (AVR), coronary bypass, ascending aortic conduit) and 6 of these pat. had a second cardiovascular operation (3 due to Typ A AD after AVR). During TEE examination one or more boli of echocardiographic contrast media (CM; Optison®) able to cross the pulmonary vascular bed were given intravenously.

Results: An AD and/or partial or partially covered perforation could be detected in 13 pat. (n=6 Typ A; n=5 Typ B; n=1 Typ B and perforation; n=2 perforation of the aorta) and in 3 preoperated pat. with aortic conduits perforation sites could be diagnosed. After intravenous administration of CM there was an initial shadowing of the ascending aorta by CM in the left atrium and the pulmonary artery. This effect disappeared after a few seconds and the lumen and wall of the ascending and descending aorta could be visualized with a clear delineation of the aortic wall especially in preoperated pat. and pat. with large aortic aneurysms. Only with CM a dissecting membrane could be diagnosed or better visualized in 4 pat., and in all pat. more entrys/reentrys could be detected. In preoperated pat. there was a better visualizaton of perforation sites between native aorta and aortic conduit with CM. In 1 pat. with a large aortic aneurysm only with CM thrombotic material was detected inside the aorta.

Conclusion: CM greatly improves diagnostic accuracy of TEE in pat. with suspected aortic dissection by better identification of dissecting membranes and detection of entries/reentries, perforation sites, and thrombotic material.

3424 Assessment of the pulmonary veins by transoesophageal echocardiography: determination of standard values of pulmonary venous flow and diameter

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Background: Pulmonary vein (PV) stenosis has been described as a rare complication after radiofrequency catheter ablation. Using transesophageal echocardiography (TEE) PV stenosis can be identified by increasing blood flow and decreasing vessel diameter.

Aim: For further evaluation and quantification standard values are necessary which should be determined in this study.

Methods: In 206 patients (137 men, mean age 62y) without cardiac diseases TEE was performed assessing mean (PVVm) and peak (PVVp) pulmonary venous flow velocity, velocity time integrals (VTI) and pulmonary vein diameter. All PV (left upper and lower PV, right upper and lower PV) were analysed.

Results: In 204 of 206 patients all PV could be visualized by color doppler imaging. In two patients the left and right lower PV could not be assessed. The table describes the results of all measurements.

	Left upper PV	Left lower PV	Right upper PV	Right lower PV
PVVm (cm/sec) Standard Error	32 ± 13,5	27 ± 12,1	34 ± 15,1	29 ± 8,8
PVVp (cm/sec) Standard Error	53 ± 18,8	32 ± 13,6	64 ± 28,2	53 ± 17,6
VTI (cm) Standard Error	24 ± 10,8	22 ± 10,9	26 ± 13,7	22 ± 8,7
Diameter (mm) Standard Error	13,4 ± 2,8	12,4 ± 2,6	13,6 ± 2,6	12,7 ± 2,5

Measurements of pulmonary venous flow velocities and vessel diameters by transesophageal echocardiography

Conclusion: For better evaluation and quantification of pathological pulmonary venous flow we determined standard values of mean and peak flow velocities, velocity time integrals and vessel diameters by transesophageal echocardiography.

3425 Transoesophageal echocardiography: a screening method for pulmonary venous stenosis/occlusion after catheter ablation of atrial fibrillation

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Background: Pulmonary vein (PV) stenosis has been described as a rare complication of radiofrequency treatment.

Methods: We report on 5 patients of a total of 280 who complained about dyspnea and hemoptysis during follow up after catheter ablation of atrial fibrillation. Subsequently transseptal pulmonary venous angiograms were performed followed by recanalization of 3 totally occluded PV and ballon dilatation of 2 high-degree PV stenosis. In one patient mild PV stenosis was found. Severe stenosis was angiographically defined as narrowing of more than 70%, mild stenosis of less than 50%. Transesophageal echocardiography (TEE) was performed in all 5 patients, assessing mean (PVVm) and peak (PVVp) pulmonary venous flow velocity, velocity time integrals (VTI) and pulmonary vein diameter. A control group of 206 patients was investigated by TEE to determine standard values of these parameters. Data of angiography and TEE were correlated.

Results: In totally occluded PV no flow was detectable. In all patients with severe stenosis averaged PVVm (1.74m/sec), PVVp (2.35m/sec) and VTI (133.6cm) were observed to be increased in comparison to the control group (averaged PVVm 0.28m/sec, PVVp 0.48m/sec, VTI 21cm). Averaged pulmonary vein diameter was less than 7mm (12mm in the control group). In the patient with mild stenosis averaged PVVm (0.9m/sec), PVVp (1.6m/sec) and VTI (60cm) were measured slightly increased. TEE showed reestablished pulmonary venous flow in all recanalized vessels. In only one case of 280 investigations a angiographically normal PV could not be visualized by TEE.

Conclusion: TEE with assessment of pulmonary venous flow parameters and vessel diameter can be used to detect pulmonary venous stenosis and occlusion after catheter ablation and is also able to serve as follow-up tool after recanalization.

3426 Evaluation of the morphological changes of the aorta and its branches by TEE in patients with Takayasu arteritis

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Background: Takayasu arteritis is a chronic inflammatory disease of unknown etiology affecting mainly the aorta and its major branches, exhibiting intimal hyperplasia, medial degeneration and adventitial fibrosis. CT and MRI were reported to be useful methods for the evaluation of the morphological changes in the aorta and its branches in Takayasu arteritis. There are no reports regarding the role of transesophageal echocardiography (TEE) in the assessment of intimal thickening of the aortic wall in these patients.

Purpose: The aim of the present study was to test the value of TEE in the evaluation of morphological properties in the aortic wall in Takayasu arteritis.

Methods: The thoracic aorta was studied in 10 female patients (mean age 34 ± 3 y) with Takayasu arteritis by TEE. Intimal thickening was defined pathologically when it reached above 3 mm.

Results: TEE revealed thickening of the intima of the thoracic aortic wall in all patients (mean maximal intimal thickening 3.9 ± 0.7mm, range 3.2-4.5 mm). Maximal intimal thickening was noted in the aortic arch in 6 patients (60%), and in the aortic arch and ascending aorta in 2 patients. In the remaining 2 patients all thoracic aortic segments were diffusely involved (4.5 mm). In these last 2 patients, intimal thickening and narrowing of the proximal portion of the cranial vessels were also demonstrated. TEE detected mild aortic regurgitation in 4 patients (40%).

Conclusions: This study demonstrates for the first time that TEE can detect intimal thickening of the thoracic aortic wall, and therefore may be a useful adjunctive tool for the diagnosis of Takayasu arteritis.

3427 Usefulness of the transoesophageal echocardiography in the monitoring of the endoluminal graft for the treatment of the thoracic aorta diseases

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Background: The implantation of transcatheter aortic endoprosthesis is an innovative and minimally invasive tecnique for the treatment of the thoracic aorta diseases. Its growing use, justified by the high rate of mortality with surgical approach, requires a careful monitoring both during its implantation to guide a correct placement and in the follow-up period to evaluate its efficacy and safety.
Aim of the study: To evaluate the usefulness of the transesophageal echocardiography (TEE) in the intra- and post-procedural monitoring of the graft implantation.
Methods: Thirty-five consecutive patients (4 F, 31 M), with prior diagnosis of aortic dissection type B of Stanford (14 pts), aneurysm of thoracic aorta (11 pts), and post-traumatic rupture of thoracic descending aorta (10 pts) have been studied. All the patients underwent deployment of endovascular stent-grafts in the descending thoracic aorta, and the procedure was entirely monitored with angiography, fluoroscopy and TEE exam. The safety of this approach has been evaluated during the follow-up period with angio-TC and TEE at six months and at 1 year after the implantation.
Results: In all the patients the intra-procedural TEE allowed an optimal visualization of the graft and its relationship with the aortic wall, playing a key-role for the correct placement of the graft in the 31.4% of cases (11 pts). Intra-procedural TEE was also determinant for the discovery of 1 case of intimal rupture in a patient with dissection and, with the help of Color-Doppler, for the diagnosis of 2 cases of leak. During the follow-up TEE showed the appearance of peri-prosthetic leaks, confirmed at angio-TC exam, in 2 patients with prior aortic aneurysm.
Conclusions: TEE has demonstrated to be an important diagnostic tool in the monitoring of aortic endoprosthesis. This simply and reliable tecnique, giving the cardiologist important anatomical and functional informations both during the procedure and later, during the follow-up, contributes to improve the safety of this new therapeutical option for diseases of the descending thoracic aorta and to promptly identify eventual related complications.

NEW MARKERS FOR STRESS-INDUCED ISCHAEMIA

3432 Vasodilator stress echocardiography: regional wall motion and/or coronary flow reserve for the diagnosis of coronary artery disease?

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Background: Vasodilator stress echocardiography allows semi-simultaneous imaging of left anterior descending (LAD) coronary flow and regional wall function.
Aim: to assess the relative (and additive?) value of regional flow and function for noninvasive identification of angiographically assessed LAD disease in patients with chest pain syndrome. Methods: 191 consecutive in-hospital patients (111 males, age=64±18 years) with chest pain syndrome and normal regional and global left ventricular function were enrolled. All underwent dipyridamole (up to 0.84 mg/kg over 10') stress echo, including wall motion analysis by 2-D echo (2DE) and coronary flow reserve (CFR) evaluation of LAD by TTE-Doppler, with or without contrast injection. A new regional wall motion abnormality in at least 2 contiguous segments was required for 2DE positivity. CFR was evaluated as the ratio of dipyridamole to rest peak diastolic coronary blood flow velocity. A CFR <2 was required for CFR positivity. All patients had coronary angiography within 15 days and a diameter reduction >50% of LAD was considered significant.
Results: Of the 191 patients, 61 had CAD, and 130 no CAD. A regional wall motion abnormality in LAD territory was present in 44, a reduced LAD CFR in 54 patients. Sensitivity for detecting LAD disease was 73% for 2DE and 87% for CFR (p=ns); specificity 91% for 2DE and 78% for CFR (p<.01); accuracy was 85% for 2DE and 81% for CFR (p=ns). The positive predictive value of 2D- echo was 80% and the negative predictive value of a normal CFR was 93%. Conclusion: CFR can be obtained during vasodilator stress echo. Its diagnostic accuracy for detecting LAD disease is lower than regional wall motion abnormalities - due to limited specificity.However, the two informations of flow and function can be additive in terms of prediction of underlying angiographic anatomy, since a positive 2D echo is more efficient to include CAD disease, and a negative CFR is more efficient to exclude it.

3433 Could we apply regional strain and strain rate measurement during all forms of stress echocardiography?

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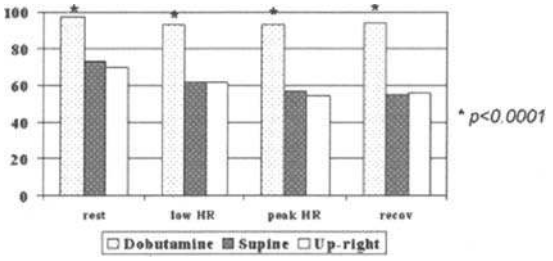
Regional strain (S) and strain rate (SR) reflect differing aspects of myocardial function. S is related to stroke volume while SR correlates better with local dp/dt. Together, they offer a new approach to understanding and quantifying normal and abnormal responses during stress echo. However, SR/S are signal noise dependent and artifacts induced by respiration during excercise stress could preclude their use.
Study Aims: To compare the feasibility of regional peak systolic (p) Velocity and SR/S data collection/analysis during up-right bicycle (Group 1, n=10), supine bicycle Group 2, n=10) and dobutamine (DSE) (Group 3, n=10) stress echo.
Methods: pVel/pSR/pS data were acquired at each stress stage for 14 segments per patient/stage.
Results: The number of analysable segments (pSR/pS) per stage was significantly higher for DSE (p<0.0001)(Fig.1). A detailed comparison of data yield for each stress modality showed that for DSE: pVel/pSR/pS traces were interpretable in 94.6% segments. (The highest number of rejected segments were in the basal and apical segments). Signal noise meant that pSR/pS responses were not interpretable in 40% of Group 1 segments (12% basal-LW, 10% apical segment-AW). In Group 2, 40% segmental responses were also un-interpretable (apical segment AW 20%; apical IW 16%). In comparison, pVel could be measured in a higher number of segments: 74%-Group 1 (highest % exclusions - apical segments of Sep and AW (22%)) and 70% Group 2 (exclusions - apical segments IW 16% - apical AW 20%).



Percentage of analysable segments.

Conclusion: The application of SR/S imaging to the quantitation of stress echo may be currently be limited to DSE as signal noise precluded adequate data acquisition during excercise. For excercise this was also true for measurement of segmental pVel response.

3434 Quantifying radial deformation: the response in regional strain rate and strain during differing types of stress exercise

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Background: It has been shown experimentally that strain rate (SR) and strain (S) parameters can quantify changes in regional radial systolic function over a wide range of heart rates and differing contractile states. For normal myocardium, SR correlates better with local dp/dt while changes in strain (S) are related to changes in stroke volume/EF. Thus peak systolic(p)SR/S measurement may offer a new approach to understanding and quantifying normal and abnormal responses during stress echo.
Study Aims: To investigate the ability of pSR/pS to quantify changes in regional myocardial function and to compare their normal responses to see if they differ during up-right bicycle (Group 1, n=10), supine bicycle exercise (Group 2, n=10) and dobutamine (DSE) (Group 3, n=10) stress.
Methods: Peak systolic (p) SR and S were acquired at each exercise stage: baseline (B), low HR=100-120 b/m (L) and peak HR=140-160 b/m (P), recovery (R). Data was acquired from parasternal long (pLax) and short axis (pSax) views from the posterior wall basal segment(BSPW).
Results: Data was obtained from 80 segments (n=10). Mean systolic values from BSPW are shown in the table (pLax; pSax).

	Group 1			Group 2			Group 3		
	Vel cm/s	SR 1/s	S %	Vel cm/s	SR 1/s	S %	Vel cm/s	SR 1/s	S %
pLax									
B	4±1	2.3±0.3	27±10	4.6±1*	2.3±0.4	36±9	3.1±1	2±0.6	30±10
L	6.6±1*	2.6±0.4	39±3	5.8±1*	3.8±1.4	48±10	5±0.8	2.6±0.7	32±13
P	11±1*	5.2±0.7	38±16	9.4±2*	4.3±0.8	48±8	7±1.6*	3.7±1*	31±13
R	4.4±1	2.6±1.2	26±8	5.8±1.4	3.1±1.4	36±13	5.5±1.8	2.3±1	32±13
pSax									
B	4.2±0.7	2.4±0.7	30±4	4.4±1.5	2.4±0.3	41±5	3.2±1	2.1±0.7	27±12
L	6.4±1*	3.6±0.7*	48±4	6±1.4*	4±0.7*	51±10*	5±0.6	2.6±1	32±12
P	11±1.1*	4.7±0.7	39±8	9±1.7*	5±0.3	49±12	7.2±2*	3.5±1*	30±14
R	4.3±1.3	2.4±0.8	30±4	5.8±0.8	3±0.9	39±7	5.5±2	2.8±1	31±13

(* p<0.005 vs baseline)

Conclusions: Independent of stress type (exercise vs pharmacologic), both pSR and pVel values increased linearly and reached a maximum at peak stress (HR=140±7). In contrast, segmental pS response was biphasic, with pS increasing during low HR stages (100±12 b/m). pS values then fell at HR>140. This biphasic S response (vs.linear SR)is due to fall in stroke volume at peak exercise.

3435 Index of postsystolic motion as a marker of the severity of stress induced myocardial ischaemia

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The aim of the study was a quantitative assessment of the impact of stress induced myocardial ischemia on systolic (S) myocardial velocities (m.v.) and index of post-systolic motion (PSM) changes during dobutamine echocardiography (DE) using pulsed wave Doppler myocardial imaging (PW-DMI).
Methods: We studied 42 patients (pts) with known or suspected coronary artery disease. In all pts DE (from 5 up to 40 mcg/kg/min, plus atropine up to 1 mg if needed) was performed. DE identified ischemia by the occurrence of wall motion abnormalities (WMA) with stress. A 11-segments left ventricular (LV) model was utilized. At baseline and after DE in each adequately visualized dyssynergic LV segment, we analyzed the presence of PSM and from apical approach, we measured peak myocardial velocity (m.v.) of systolic (S) and PSM wave using PW DMI. Index of PSM was assessed as followed: (peak S velocity at peak stress - peak velocity of PSM)/peak S velocity at peak stress.
Results: During DE 112 ischemic myocardial segments in 31 pts were detected, while in 11 pts WMA were not appeared. Out of 112 LV segments 61 (54.5%) were hypokinetic, 42 (37.5%) were akinetic and 9 (8.0%) were dyskinetic. After DE in ischemic LV segments S decreased from 8.6 ± 3.1 to 6.2 ± 3.7 cm/s, P<0.001. Value of index of post-systolic motion was significantly lower in hypokinetic than in akinetic segments (0.21 ± 0.06 vs 0.39 ± 0.11, P<0.001), in hypokinetic than in dyskinetic sements (0.21 ± 0.06 vs 0.67 ± 0.09, P<0.001) and in akinetic than dyskinetic segments (P<0.001). After DE, in segments without stress induced WMA S m.v. significantly increased (P<0.001).
Conclusion: Our data show that PSM develops actually in segments with stress provoked myocardial ischemia and that index of post-systolic motion can be used as a marker of the severity of myocardial ischemia.

3436 Quantitative dobutamine stress echocardiography based on a new automatic analysis algorithm for tissue Doppler data

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The main limitation of dobutamine stress echocardiography (DSE) is its subjective interpretation. Tissue Doppler imaging (TDI) has been used with promising results for quantitative analysis of DSE. However, it required extensive time consuming analysis.
We evaluated a new analysis algorithm which allows acquisition of TDI data in the background of the 2D image during DSE and subsequent instantaneous automatic analysis of TDI information.
Methods: In 30 consecutive patients undergoing coronary angiography DSE was performed with color TDI data being acquired in the background. An analysis algorithm was used which allows automatic comparison of obtained peak systolic tissue velocities with expected "normal" peak systolic tissue velocities and subsequent color coding of areas reaching the normal value. Quality of 2D image with simultaneous acquisition of TDI data was assessed on a three grade score (1: worst to 3: best) and compared with image quality of mere 2D image acquisition. Results of DSE based on quantitative TDI analysis were compared to DSE results based on visual 2D assessment.
Results: Image quality of 2D images with simultaneous acquisition of TDI data was almost similar compared to mere 2D image acquisition (2.68±0.37 vs 2.74±0.36, respectively, p=n.s.). There was agreement between DSE test results based on visual evaluation of 2D images and DSE test results based on color coded automatic analysis of quantitative TDI data in 87% of patients (kappa= 0.58). Accuracy of DSE for detection of coronary artery disease defined by coronary angiography with analysis of TDI in addition to 2D images was 83% vs. 78% for analysis of 2D images alone (p=n.s.).
Conclusion: Simultaneous acquisition of TDI and 2D data is highly feasible as it allows rapid acquisition of TDI data without a substantial loss in 2D image quality. Automatic analysis of TDI data allows rapid quantitative analysis of regional myocardial function at peak stress. It increases the security on the accurate interpretation of DSE test results.

3437 Pulsed Doppler myocardial imaging can help to distinguish symptomatic from asymptomatic myocardial ischaemia during stress echocardiography

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Objective: to compare regional systolic and diastolic myocardial velocities (m.v.) changes induced by symptomatic or asymptomatic myocardial ischemia (m.i.) during stress echocardiography using pulsed wave Doppler myocardial imaging (PW DMI).
Methods: In the study group of 95 pts with known or suspected CAD exercise stress echocardiography (ExE) was performed. ExE identified ischemia by the occurrence of wall motion abnormalities (WMA) with stress. Apical views were used to assess m.v. (Acuson-Sequoia, PW DMI) on baseline and at the peak stress. The sample volume was placed in each of 11 segments in which the left ventricle was divided, and we calculated peak m.v. of systolic (S), early (E) and late (A) diastolic waves and their ratio E/A.
Results: During ExE 182 ischemic myocardial segments in 65 pts were detected (118 segments in 36 pts with symptomatic and 64 segments in 29 pts with asymptomatic m.i.), while in 30 pts WMA were not appeared. After ExE value of wall motion score and number of ischemic segments per patient were significantly bigger in pts with symptomatic than in pts with asymptomatic m.i. (P<0.02 and P<0.01). In segments with ExE provoked symptomatic and asymptomatic WMA, DMI variables showed similar dynamics: E decreased by 25% and 18.1%, A increased by 7.7% and 6.1%, ratio E/A decreased by 28.3% and 23.5% and S decreased by 11.1% and 8.2% compared with baseline values. After ExE the rate of E and E/A ratio reduction in ischemic segments was significantly higher in pts with symptomatic than in pts with asymptomatic m.i. (P<0.005 and P<0.02).
Conclusion: Our data showed that both types of m.i. have similar effects on DMI variables, but changes are more pronounced in symptomatic m.i. Reduction of E wave and E/A ratio in ischemic segments are significantly higher in symptomatic than in asymptomatic m.i.

POSTER DISPLAY VI

MODERATED POSTER SESSION VI

P3438 A third family with aortic dissection/aneurysm and patent ductus arteriosus association. Is there a new syndrome?

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We report a large family presenting an unusual association of familial thoracic aortic dissection/aneurysm (TAD/TAA) and patent ductus arteriosus (PDA).
Subjects and methods: this family composed of 179 members was ascertained from a single asymptomatic probant because of his familial history. Forty first-degree relative subjects from three different generations have been enrolled in a clinical investigation protocol composed of two parts:
– A medical questionnaire concerning available medical records, state of health and allowing to investigate the familial history. A standardized clinical examination focused on classical signs of Marfan and Ehlers-Danlos syndromes.
– An annual long-term follow-up based on: standardized cardiovascular examination, transthoracic echocardiography and a thoracic MRI, completed by transesophageal ultrasonography when necessary, allowing the accurate measurement of the aorta, great vessels and heart. At the time of the inclusion, blood measurements of total and LDL-HDL cholesterol, triglycerides and glucose were performed
Results: 9 cases of TAD and TAA among this family 4 TAD (2 males and 2 females) and 5 TAA (4 males and 1 female). The 5 cases of TAA were discovered by systematic screening in asymptomatic individuals. 8 cases of PDA (newborn until 27 years-old) without any particular neonatal context were noted in this family 2 of them were discovered by the study at age 3 and 5. Among the 5 cases of stroke, two of them had a documented intracranian carotid aneurysm. The distribution of TAA/TAD, PDA and vascular events within the family was compatible with an autosomal dominant with incomplete penetrance pattern of inheritance as it is in both families previously described in the literature. For each affected individuals, there was no argument for Marfan, Ehlers-Danlos or CHAR syndromes. There was no particular familial context of arterial hypertension or atherosclerosis.
Conclusion: According to the literature, familial aortic dissection/aneurysm with patent ductus arteriosus may be a new entity due to a common genetic defect that has to be discovered.

P3439 Evidence for increased circulating apoptotic endothelial cells in patients with coronary artery disease

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Endothelial dysfunction in coronary artery disease (CAD) correlates with enhanced oxidative stress and increased cytokine levels, which both induce apoptosis of endothelial cells in vitro. However, evidence for the occurrence of increased endothelial cell apoptosis in CAD was documented previously only in animal models or by post mortem analysis of vessel tissue. Therefore, we developed a method for the assessment of the level of apoptotic circulating mature endothelial cells in patients with CAD in vivo by 4-channel flow cytometry.
To distinguish mature from progenitor endothelial cells, we incubated venous blood samples following red cell lysis with a perCP-linked antibody against CD45. Among CD45-negative cells, we defined cells being double-positive for the endothelial cell-specific epitopes vWF (stained with a PE-linked anti-vWF antibody) and CD146 (FITC channel) as mature endothelial cells. Levels of circulating mature endothelial cells were profoundly increased in patients with CAD (mean±SEM=110±22/μl, n=43) compared with healthy control subjects (15±6/μl, n=15, $p<0.001$). Using the fourth fluorescence channel, we measured endothelial cell apoptosis by APC-labelled annexin V staining. Levels of apoptotic endothelial cells were ~50-fold increased in CAD patients (26±9% vs. 0.5±0.2%, control, $p<0.001$). The number of apoptotic circulating endothelial cells significantly increased with age ($r=0.33$, $p<0.02$). In a subset of patients, we determined the number of endothelial progenitor cells (EPC), which we defined as cells positive for both, the progenitor marker Ac133 and the endothelial cell marker KDR. In contrast to mature endothelial cells, endothelial progenitor cells (EPC) were decreased in CAD (3.3±1.3%, n=16 vs. 34±11% in control, n=6, $p<0.001$) and decreased with age ($r=-0.60$, $p<0.005$).
In conclusion, we established a novel flow cytometry-based method to analyze circulating endothelial cells from venous blood samples. The allover number of mature endothelial cells is increased in the circulation of patients with CAD, whereas these patients have markedly decreased levels of endothelial progenitor cells. By assessing annexin V binding of endothelial cells, these data also provide clinical evidence for the occurrence of endothelial cell apoptosis in patients with CAD.

P3440 100 consecutive cardiac myxomas: a surgical pathology experience

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Background: The role of pathologist in the field of primary cardiac tumors has been evolving and it is primarily carried out in the in vivo diagnosis of surgically resected specimens to establish tumor histotype, to identify malignancy and to make differential diagnosis with other masses. Design and Results. In the period 1970-2000, 140 surgically resected primary cardiac tumors have been studied by histology and immunohistochemistry. Twelve (8.5%) turned out to be malignant and 128 (91.5%) benign. Among the malignant tumors, 3 were endocavitary and clinically misdiagnosed as myxoma. 100 (69%) of all benign cardiac tumors were eventually diagnosed as myxomas, coming from 99 pts, 34 male and 65 female, mean age 52±15 (range 6-85). Myxoma was located in the left atrium in 78 cases, right atrium in 19, right ventricle in 2 and left ventricle in 1. Myxoma was an incidental finding at echo in 26% of pts; in the remaining pts constitutional and obstructive symptoms were present in 81% and 40%, respectively; embolism occurred in 23%. The surface was smooth or gently lobulated in 65% and villous in 35%; superficial thrombus was present in 11% and haemorrhage in 18%. Eight myxomas (mean age 60±9 yrs, $p<0.01$ vs remaining pts) showed heavy partial or diffuse calcification at x-Ray ("lithomyxoma"). At histology, myxoma showed pseudovascular aspect in 70%, both pseudovascular and secretive aspects in 20% and isolated stellate cells embedded within a myxoid background in 10%. At immunohistochemistry, myxoma cells showed positivity for vimentin (100%), alfa smooth muscle actin (50%), neurofilaments and S100 (50%). Conclusions. Myxoma represents the most common primary cardiac tumor removed at surgery (70%) and mostly occurred in middle-ages women. One fourth are incidental discoveries at 2-D echo. Thorough histological examination is mandatory to differentiate myxomas from endocavitary malignancies.

P3441 Pregnancy outcome in women with valve prostheses. A comparative study

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There is still some controversy concerning the evolution of pregnancy in women with valve prostheses. Our aim was to study the clinical course of women with valve prostheses during pregnancy and identify possible prognosis factors.
Methods: We studied 125 pregnant women with valve prostheses: 91 with bioprostheses (BP)(mean age=26.5±5.7)and 34 with mechanical prostheses(MP)(mean age= 25.5±6.4.During gestation we assessed the prostheses-related clinical events as congestive heart failure; thrombo-embolism; infective endocarditis; reoperation and maternal death; and prostheses dysfunction as stenosis, rupture, calcification, thrombosis and/or vegetation. Routine pre-natal care included echodopplercardiogram and substitution of coumadin by heparin during the first trimester and after 36 weeks of gestation in MP group.
Results: Ninety-two (73.6%) patients had an uneventful course. The events are summarised in table. Four maternal deaths were due to prostheses dysfunction (calcification in BP and thrombosis in MP).There were 117 (92.8%) alive newborns, 30 of them premature babies, and two with fetal neurological malformation, both from mother who suffered reoperation. Among the events the incidence of heart failure($p=0.02$), prostheses dysfunction ($p=0.02$) and reoperation ($p=0.03$) were higher in BP group. The incidence of total events was higher in pregnancy which occurred after 60 months from prostheses implantation for BP (43.3% vs 16.4%) and MP (50.0% vs 10.0%) ($p<0.01$).

Incidence of events during study

Events n/%	HF	IE	Thromb	Dysfunction	Reoperation	Death
BP 91pts	17/18.9*	3/3.0	5/5.5	16/17.6*	12/13.2*	3/3.3
MP 34pts	0/0	1/2.9	4/11.7	1/2.9	2/5.9	1/2.9

*$p<0.05$. HF-heart failure;IE - infective endocardites; Thromb-thrombosis and embolism episode; dysfunction- prostheses valve dysfunction; reoperationduring gestation; death - maternal death.

In conclusion: Pregnancy in patients with valve prostheses, both mechanical or bioprostheses, was associated to substantial maternal and fetal risks. Prostheses dysfunction and reoperation were more frequent in bioprotheses group. Worse maternal prognosis, for both groups, was related to the time delay from prostheses implantation to gestation.

P3442 Fibrinolysis of mechanical prosthetic valve thrombosis. A single center study about 127 cases

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Fibrinolytic treatment of prosthetic heart valve thrombosis (PHVT) appears to be an attractive alternative, to surgery, but is still controversial because of the risk of embolism. Therefore, we analyzed the results of fibrinolysis in a large group of PHVT. **Methods:** 110 consecutive patients presenting with 127 instances of PHVT (79 mitral, 46 aortic, 1 tricuspid and 1 mitro-tricuspid) were treated with fibrinolytic treatment in the same center between 1978 and 2001. The diagnosis of PHVT was established by fluoroscopy and/or echocardiography. Obstructed valves consisted of 79 bileaflet valves and 48 tilting disc, and fibrinolytic agents of streptokinase (SK) 49 cases, urokinase (UK) 41 and rtPA 37 times. A second fibrinolytic treatment was consecutively infused in 38 patients and a third in 11. The efficacy of treatment was assessed by well established hemodynamic parameters derived from echo as well as by clinical evaluation. **Results:** Complete resolution of hemodynamic abnormalities was seen in 90 (71%) episodes, partial resolution in 22 (17.3%) and no change in 15 (11.8%) after one or several consecutive fibrinolytic regimen. The efficacy of SK and rtPA, as the initial fibrinolytic agent was superior to UK in terms of valve reopening $p = 0.06$. Sixteen patients died (11.8%), death was significantly higher in NYHA functional classes III and IV. An haemorragic complication was observed in 6 pts (4.7%), nineteen (15%) documented embolic events occurred during fibrinolytic treatment (8 stroke, 6 TIA, 5 peripheral arterial). Finally, PHVT reccured in 24 (18.9%) cases treated with fibrinolysis.
Conclusion: The results of this extensive single center experience indicates that fibrinolytic treatment is effective in most cases of PHVT regardless of prosthesis or site involved. SK and rtPA are superior to UK in terms of valve reopening. However, a substantial incidence of embolism, haemorrhage and death occurred with lytic therapy of PHVT, limiting its application to patients at high risk with alternative treatment.

P3443 Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo

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Patients with cardiovascular diseases (CVD) frequently complain of erectile dysfunction especially when treated with beta-blockers. In order to assess whether the effect of beta-blockers on erectile dysfunction is, in part related to patient knowledge of the drug side effects 96 male patients with CVD entered a double-blinded parallel study. Thirty-two patients atenolol 50 mg (A) without knowledge of the drug they were administered, 32 received A knowing that the drug was a beta-blocker and 32 received A knowing that the drug they were taking was a beta-blocker and that it could have given erectile dysfunction. After 3 months patients were administered a quality of life questionnaire containing questions about erection. The incidence of erectile dysfunction was 3% in the group not knowing which drug they were taking, 16% in the group knowing that they were receiving a beta-blocker and 30% in the group also knowing the side effects of the drug ($p<0.01$). Sildenafil citrate and placebo were equally effective in reversing erectile dysfunction in all but one patient. In conclusion in male patients with CVD the report of erectile dysfunction after therapy with beta-blockers is largely related to patient knowledge of the drug side effects as it is almost always completely reversed by placebo.

P3444 Identification of 17 new mutations associated with catecholaminergic polymorphic ventricular tachycardia (CPVT) and their phenotypic variation

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Background: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disorder. It is characterized by normal QT intervals and adrenergic induced ventricular tachyarrhythmias, which lead to syncope and sudden death in young patients with structurally normal hearts. So far, autosomal dominant missense mutations in RYR2, the gene encoding the cardiac ryanodine receptor type 2, and an autosomal recessive missense mutation in the cardiac calsequestrin gene (CASQ2), have been reported to be responsible for this disease. **Methods:** We collected 35 CPVT probands and their family members from France and Netherlands. The phenotypes were ascertained by ECG and stress test. Probands were screened by exonic PCR amplification and uni-directional sequencing. After positive identification of an aberrant sequence, at least 200 control alleles were screened using SSCP or RFLP. **Results:** We have identified 13 new missense mutations in the RYR2 gene of CPVT probands. All these mutations occur at evolutionary conserved positions across the RyR proteins of multiple species. The mutations appear to be grouped into three distinct regions, suggesting a functional importance of these regions for all RYR genes. In addition, sequencing of the cardiac calsequestrin gene (CASQ2) revealed four new mutations: two nonsense of which one is homozygous, one splice site and one missense mutation. Two CASQ2 mutations have an autosomal dominant and two have a recessive mode of inheritance. The 13 RYR2 mutations show a high degree of penetrance, apart from two families, which have incomplete related penetrance. In contrast the CASQ2 mutations including the nonsense mutations show reduced penetrance.
Conclusion: We found 17 new mutations in the RYR2 and CASQ2 genes in 35 CPVT families. This indicates the feasibility of pre-symptomatic detection of CPVT. Furthermore, we report the first homozygous nonsense mutation of CASQ2 as well as autosomal dominant mutations. In addition we can now compare the inter- and intra phenotypic variations of CPVT between the various RYR2 and CASQ2 mutations.

P3445 Typical slow-fast nodal re-entry tachycardia in paediatric age: utility and risk of radiofrequency catheter ablation

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Background: Typical slow-fast nodal re-entry tachycardia (NRT) is a common rhythm disorder in children and in young adults. Radiofrequency catheter ablation (RFCA) procedure has a potential increasing risk due to the small dimension of AV node, the little distance of fast and slow pathways and the growth of cardiac structures.
Methods: In the last 12 month, 14 patients (6M/7F aged 11±2.4 years) underwent electrophysiological study (EPS) + RFCA for NRT All procedures were performed in general anaesthesia. Vascular accesses used in all patients were: right femoral and right subclavian veins.
Results: Time of procedure, including anaesthesia induction, was 70±15 min. Time of radiation exposure was 15±5min. In all patients we targeted the slow pathway with a combined anatomical and electrophysiological approach. RF delivery sites were: point 9-10 in 9 pts and point 7-8 in 4 pts. Accelerated junctional rhythm was observed in 8/13 pts. Basal AH (67 ± 18 msec) and HV (39 ± 2.8) intervals and Wenckebach point (<319 ± 51) were unmodified after procedures. Follow up: All patients performed a non-invasive evaluation 30 days after RFCA. Echocardiography and Holter-ECG were normal; no arrhythmia was induced during stress test. Three months after RFCA we performed a control EPS. In one pts there was a recurrence of NRT, so a new RF delivery was required. In 5/14 pz no tachycardia could be induced, although a ono-to-one anterograde slow pathway has been documented.
Conclusion: RFCA is a highly-effective tool for NRT even in paediatric age.

P3446 Effect of glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary intervention after pretreatment with aspirin and clopidogrel

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Objective and background: The present study was designed to investigate 1) the amount of troponin T release after non-acute, elective PCI in patients pretreated with aspirin and clopidogrel and 2) the effect of additional glycoprotein (GP) IIb/IIIa receptor inhibiton on troponin T release in detail.
Methods: The TOPSTAR - trial is a double blind, randomized, placebo-controlled prospective trial on 109 patients with stable angina pectoris undergoing elective PCI. All patients were pretreated with aspirin and clopidogrel. After bolus application PCI was performed followed by an 18 hour continuous infusion of the study medication. Primary endpoint of the study was incidence and amount of release ischemic paramters (troponin T (TnT) and creatinkinase (CK, CK/MB)) after elective PCI.
Results: Platelet function was inhibited by 90% throughout administration of tirofiban. Within the first 12 hours after PCI Troponin release was detected in 63% of the patients receiving placebo (P) and in 40% of the patients receiving Tirofiban (T) ($p<0.05$), within 24 hours in 69% (P) and 48% (T) ($p<0.05$) and after 48 h in 74% (P) vs. 58% (T) ($p<0.08$) of the patients. No differences were observed regarding major bleeding, intracranial bleeding or non-hemorrhagical strokes. After 9 months a reduction of combined death/myocardial infraction/target vessel revascularisation could be observed in the tirofiban group ((T) 2.3% vs. (P) 13.04%, $p<0.05$).
Conclusion: TnT release occurs after successful intervention in 74% of the patients after 48 hours undergoing elective PCI even after pretreatment with aspirin and clopidogrel. The glycoprotein IIb/IIIa receptor antagonist Tirofiban is able to decrease the incidence of troponin release after PCI significantly in this patient population probably due to improved myocardial macro- and microcirculatory perfusion and might influence long term outcome.

ATRIAL FIBRILLATION TREATMENT

P3447 Catheter ablation of drug induced atrial flutter: impact on atrial fibrillation recurrences and quality of life

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Background: Radiofrequency (RF) catheter ablation of isthmus-dependent, antiarrhythmic drug (AAD)-induced atrial flutter (AFL, "hybrid-therapy") is clinically relevant in the treatment of atrial fibrillation (AF). The aim of this study was to analyse the long-term preventive efficacy of this "hybrid-therapy" and its effect on AF-symptoms and quality of life (QoL).
Methods: Thirty-two patients (pts; age: 65.0±7.2 years; 9 women; left ventricular ejection fraction: 62.8±15.2%; structural heart disease (14), idiopathic AF (18)) were monitored after isthmus-ablation of AAD-induced AFL and continuation of this AAD treatment for AF-recurrences over a mean follow-up of 21.6±9.7 months. AF characteristics and symptoms as well as QoL before and after ablation were retrospectively evaluated by the "SF-36"-questionnaire, "symptom checklist" and "AF severity scale".
Results: 7 of 32 pts (21.8%) remained free of AF recurrences after hybrid therapy. From 25 of 32 pts (78.2%), who demonstrated AF-recurrences during follow-up, 19 (76%) demonstrated a decrease in frequency of symptomatic AF-episodes, from 5.8±5.9 before to 0.4±0.8 episodes/week after ablation ($p<0.05$). A significant decrease in AF episodes duration was documented in 17/25 pts (68%), from 7.0±1.8 to 3.3±1.7 on an episode duration scale from 0 to 9. The symptom checklist demonstrated a significantly attenuated AF-symptomatology in 17/25 pts (68%) following ablation (44.2±27.5 versus 20.3±13.0 scores, p=0.006). Furthermore, in the study population 7 out of 8 categories of the SF-36 questionnaire were significantly improved; only the bodily pain score did not reach significant improvement.
Conclusions: The pharmacological and ablative hybrid therapy was a "curative" treatment in 21.8% of entered study population, however 78.2% of patients demonstrated AF-reoccurrences during long-term follow-up. Hybrid-therapy significantly reduced the mean number and duration of symptomatic AF-episodes as well as AF-correlated symptoms in patients with AF-recurrences. 4. This approach resulted in an significant QoL-improvement. Even when this variant of hybrid therapy for AF treatment is semicurative, it offers a clinically valuable tool in selected patients.

P3448 Fluctuations of autonomic tone before onset of paroxysmal atrial fibrillation

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Background: Mechanisms favouring the occurrence of paroxysmal atrial fibrillation (PAF) are complex and poorly defined. This study was designed to analyse dynamic changes in autonomic tone preceding the onset of PAF in a large group of unselected patients.
Methods and Results: Holter tapes from 77 consecutive patients (63 male, 14 female, mean age 58 ± 12 yrs) with PAF were analysed. A total of 147 episodes of sustained PAF (>30 min) were recorded and submitted to time-domain and frequency-domain heart rate variability (HRV) analysis. Six periods were studied using repeated measures ANOVA: the 24-hour period, the hour preceding PAF, and the 20 minutes prior to PAF divided into four 5-minutes periods. In the time-domain, a linear decrease in mean RR interval from 925 ± 16 to 906 ± 16 ms ($p<0.0002$) was observed before onset of PAF together with a significant increase in SDNN from 65 ± 4 to 70 ± 4 ms ($p<0.02$). In the frequency-domain, a significant increase in high-frequency (HF, HF-NU) components was observed before PAF ($p<0.001$ and <0.0001 respectively), together with a progressive decrease in low frequency components (LF, LF-NU) components ($p<0.0001$ and < 0.004 respectively). The LF/HF ratio showed a linear increase until 10 minutes prior to PAF followed by a sharp decrease immediately before PAF, suggesting a primary increase in adrenergic tone followed by a marked modulation towards vagal predominance. No difference was observed in these HRV changes between patients with "lone" PAF and patients with structural heart disease, nor between diurnal and nocturnal episodes of PAF.
Conclusion: The occurrence of PAF greatly depends on variations of the autonomic tone with a primary increase in adrenergic tone followed by a abrupt shift towards vagal predominance and this pattern is observed both in patients with "lone" atrial fibrillation and in patients with structural heart disease.

P3449 Seasonal variability and impact of non-cardiac factors on clinical presentation and management of AF in the emergency department (GEFAUR-2)

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PURPOSES: To determine and analise the influence of seasonal variability and the impact of non-cardiac factors (mainly respiratory tract infections, obstructive pulmonary diseases and its treatment) on the clinical features, management strategies and outcome of patients(pts) with atrial fibrillation(AF) in the Emergency Department(ED).METHODS: Prospective multicenter observational case-control study performed in the ED of 12 Hospitals in Madrid, Spain in Feb-2001. All patients with AF diagnosed in an ECG obtained in the medical area of the ED were included. Clinicoepidemiological data, management,outcome and patient's destination were recorded.Control group: GEFAUR-1 (prospective multicenter study performed in the same EDs,Jul-2000 with the same methodology,1178 pts).RESULTS: 301 pts were included, mean age 75y. There were a higher prevalence of males (48 vs.40%, p=0.01, OR=1.35) and ischemic heart disease (45 vs.30%, $p<0.001$, OR=1.9) in winter although overal structural cardiopathy (54 vs.47%, p=0.04,OR=1.3), hypertensive cardiopathy (16vs.9%,p=0.02,OR=1.95) and pts unabled(47% of the disabled vs. 30%, p=0.002,OR=2.68) were more frequent in summer.Dyspnea (34vs.28%,p=0.03,OR=1.33), chest pain (22 vs.13%,$p<0.001$, OR=1.85)dizziness (15 vs.10%,p=0.02,OR=1.53) and casual finding (5 vs.2%,p=0.002, OR=2.4) were more frequently the main presenting symptom in winter. There were a higer number of AF > 48h duration in summer (50vs.40%) and of unknown duration in winter (40vs.29%,p=0.01,OR=2.13). Stroke prevention was more frequently performed in winter (44 vs.37%, p=0.03, OR=1.31) due to anticoagulation (32 vs.23%, p=0.002, OR=1.56). Admission was more frequent in winter (54 vs.46%, p=0.002, OR=1.48), due to cardiac and thromboembolic complications ($p<0.001$). No differences were found on age, on previous AF, stroke, diabetes, thyrotoxicosis, hypertension, other heart diseases or current treatment for AF,on diagnosis of heart failure, hemodynamic compromise or secondary (non cardiac) AF(4%, mainly related with fever), on rate control/cardioversion strategies,in the relieving of the symptomatology,or ED length of stay.CONCLUSIONS:Fever is the main non-cardiac factor related with AF in the ED.Non-cardiac factors have no influence on clinical presentation and management of AF.Seasonal variability influences clinical presentation (ischemic heart disease and its related symptomatology), AF duration, Stroke prevention and admission rate (all of them more prevalent in winter). However, its impact on the overal management of AF in the ED is lesser than currently assumed.

P3450 Propafenone-sotalol: which is preferred in atrial fibrillation, for the maintenance of normal sinus rhythm

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The aim of this prospective, randomized, single blind, trial was to compare the long-term efficacy and safety of propafenone and sotalol, in maintaining normal sinus rhythm in patients with recurrent, symptomatic atrial fibrillation.
Methods: We studied 143 consecutive patients (70 men, mean age 62.9 ± 9.3 years) with recurrent, symptomatic atrial fibrillation. After restoration of normal sinus rhythm, 73 were given propafenone (450 mg/day) and 70 received sotalol (320 mg/day). End point of the study was recurrence of atrial fibrillation or occurrence of side effects necessitating discontinuation of medication. Follow up clinical evaluations were conducted at the 1st, 2nd, 4th and 6th month and at 3-month intervals thereafter. The proportion of patients remaining in sinus rhythm without side effects was calculated for the two groups using the Kaplan-Meier method.
Results: The two groups were comparable in terms of sex, age, left atrial size, left ventricular ejection fraction, pattern of AF, percentage of patients with underlying heart disease and time from initial diagnosis of AF.
The average follow up time for the non end-point patients was 26 ± 11 months for the propafenone group and 19 ± 10 months for the sotalol group.
Thirty-seven of the 73 patients (50.68%) receiving propafenone relapsed to atrial fibrillation after an average of 7 ± 6 months, compared to 47 of the 70 patients (67.14%) given sotalol, after an average of 7 ± 5 months (x^2: 4.82, $p< 0.028$). Five patients on sotalol (all of them in normal sinus rhythm) and 5 patients on propafenone (3 of them in normal sinus rhythm) experienced side effects necessitating withdrawal of medication. (x^2: 6.26, p: 0.0123 for atrial fibrillation-side effects free patients). Sex, age, atrial fibrillation pattern and left atrial diameter did not influence progression to atrial fibrillation-side effects in either group.
Conclusions: Propafenone is more effective than sotalol in the long-term prevention of side effects-free recurrent symptomatic atrial fibrillation.

P3451 Long-term results of hybrid therapy for the management of recurrent atrial fibrillation

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Objective: With the purpose of maintaining sinus rhythm in patients (pts) with recurrent atrial fibrillation, sometimes antiarrhythmic drugs (AAD) convert atrial fibrillation (AF) into atrial flutter (AFL). Combination of AAD and radiofrequency ablation (RFA) of the right atrial isthmus, has become a treatment option for these patients. Effectiveness of this treatment and determinants of AF recurrence during long term follow up are yet to be established.
Methods and Results: We analysed clinical and electrophysiological data of 100 consecutive pts with history of recurrent AF, who underwent isthmus RFA of AAD induced AFL. Mean age was 63±1.1 years and 78% of pts were male. Unsuccessful RFA (18%) was significantly higher (RR=2.17) in pts with atypical AFL. Mean follow up was 514±41 days. AFL recurred in 19% of the pts and AF as a sole arrhythmia in 23%. Sixty percent of pts were free of AF and AFL during follow up. Six percent of patients required implantation of a permanent pacemaker. Age, gender, type of AFL, presence of structural heart disease (43%), left ventricular ejection fraction (51±2%) and left atrial dimensions were not predictive of AF recurrence.
Conclusion: 1) Hybrid pharmacological and ablative therapy is effective in maintaining sinus rhythm during long term follow up in pts with recurrent AF and AAD induced AFL. 2) No clinical or electrophysiological variable predicts long term AF recurrence.

P3452 Dual defibrillator improves quality of life and decreases resource utilization in patients with drug refractory atrial fibrillation

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Aim of the study was to evaluate the impact of the dual defibrillator on quality of life and resource utilization in patients with drug refractory atrial fibrillation (AF) with no prior ventricular arrhythmias.
Methods: 40 patients (28 M, mean age 64±10) received a dual defibrillator Medtronic 7250. AF was persistent in 24 (60%) and paroxysmal in 16 (40%). 13 (32.5%) had sinus bradycardia. 26 were in NYHA class I, 11 in class II, 3 in class III.
Results: The follow-up lasted 12±6 months (range 3-28). 34 patients (85%) had AF recurrences. 1652 atrial episodes were detected and treated by the device. Anti-tachy-pacing success rate was 77% on atrial tachycardia (AT) and 32% on AF. Atrial shock was 84% successful on AT and 90% on AF. No patient had sustained ventricular arrhythmias. Comparing the year after implant with the year before, external cardioversions decreased from 2.1±2.3 to 0.1±0.3 and hospitalizations due to AF from 1.5±2.1 to 0.4±0.8 (p<0.01, both. In Table 1 Symptom Checklist Questionnaire results at pre-implant and after 12 months are reported, while Table 2 shows the SF36 Quality of Life questionnaire results.

Table 1. Symptom Checklist Questionnaire results

Item	Number	Frequency	Severity
Pre-Implant	8.6±3.0	16.9±11.0	15.8±10.5
12 months	6.3±3.1	13.0±10.3	10.6±6.1
p	<0.05	<0.05	<0.05

Table 2. SF36 QoL scores

Item	A	B	C	D	E	F	G	H
Pre-implant	64	30	75	59	45	79	69	67
12 months	84	77	83	58	55	79	73	64
p	<0.05	<0.01	ns	ns	ns	ns	ns	ns

A = Physical functioning; B = Role physical; C = Bodily pain D = General health; E = Vitality; F = Social functioning; G = Role emotional; H = Mental health.

Conclusions: Dual defibrillator was effective in treating drug refractory AF and had a favourable impact on patient quality of life and resource utilization.

P3453 Early atrial shock delivering reduces atrial fibrillation burden and hospitalizations in patients wearing a dual defibrillator

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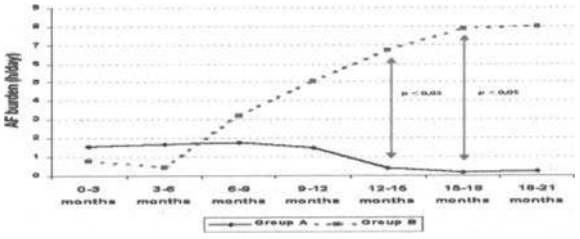
Aim of the study was to evaluate the impact of early atrial shock delivering on atrial fibrillation (AF) burden and hospitalizations in patients without ventricular tachyarrhythmias.
Methods: 40 patients (28 M, mean age 64±10) with drug refractory AF received a dual defibrillator Medtronic 7250. 24 (60%) had persistent AF and 16 (40%) paroxysmal AF. During the year before implant, they had on average 2.1±2.2 external cardioversions and 1.5±2.0 hospitalizations due to AF. One month after implant they were divided in two groups (20 patients each): group A, who accepted atrial shocks, were assigned to early delivering of atrial shock after AF onset, either automatically, by using patient activator, or in hospital, manually delivered within 12 hours; group B, who did not accept shocks, had antitachypacing therapies activated but atrial shock switched off. The groups did not differ in pre-implant characteristics.
Results: The follow-up lasted 12±6 months (range 3-28). 34 patients (85%) had AF recurrences. AF burden (hours/day) during the follow-up (months) is showed in the picture below. Hospitalizations due to AF decreased from 1.8±2.6 to 0.3±0.4 (p<0.05) in the group A and from 1.2±1.3 to 0.6±1.2 (p=n.s.) in the group B.



Burden trend.

Conclusion: In patients wearing a dual defibrillator early delivering of atrial shock reduced AF burden and AF related hospitalizations. Prevention of atrial remodeling may explain our results.

P3454 Proportion of symptomatic and asymptomatic episodes of atrial fibrillation after catheter ablation

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Background: The detection of asymptomatic episodes of atrial fibrillation (AF) is essential for assessment of success rate. The proportion of asymptomatic patients with further persistent AF after catheter ablation is still unknown.
Patients/Methods: Highly symptomatic patients (n=30, age 55± 5.8 years) with refractory paroxysmal AF lasting 5.6 ± 5.2 years and 32± 15 attacks within 3 months before ablation were included. Patients with cardiovascular diseases except arterial hypertension were excluded. Catheter ablation of AF was performed by creating linear lesions or isolation of pulmonary veins. After catheter ablation of AF the patients were investigated with a new event-recorder system (CardioRec, AD-Elektronik, Wetzlar, Germany) featuring both automatically triggered and patient activated recording.
Results: The event-recording was performed for 3.9 ± 1.5 weeks after catheter ablation (mean follow-up time 15.9 ± 2.5 months). 17/30 patients had further symptomatic attacks of paroxysmal AF while 10 patients had clinically no further attacks of paroxysmal AF and 5 (18%) asymptomatic patients with recurrent AF could be detected by automatically triggering mode of the event-recorder.
Conclusion: After catheter ablation of AF asymptomatic attacks of AF may still exist. For assessment of success after catheter ablation of AF the detection of asymptomatic episodes is essential. The use of an automatic event-recorder system for verification of the success rate is recommended.

P3455 Which patients are more likely to be cardioverted in the emergency department when atrial fibrillation arises? The GEFAUR-1 study group

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Purposes: To analyse cardioversion eligibility criteria of patients with atrial fibrillation(AF) in the Emergency Department(ED),to determine the therapeutic regimens for AF in the ED. To study the risk factors, clinicoepidemiological data and other selection criteria related with each sinus rhythm restoration (SRR) strategy.
Methods: Prospective multicenter observational study performed from Jun, 15 to Aug, 1 2000 in the ED of 12 referral hospitals in Madrid, Spain. All medical patients with AF achieved in an ECG obtained in the ED were included. Epidemiological and clinical data, risk factors for AF, previous and ED treatments, symptomatology, outcome and destination from the ED were recorded. No management recommendations were made. A multivariate analysis was performed to identify the variables related with SRR in the ED.
Results: 1178 episodes of AF were recorded.There were 246(21%) eligible patients for cardioversion (those with AF duration <48 hours).In this cardioversion-eligible group, SRR was attempted in 119 (42%) patients. In the resting 143(58%) cardioversion eligible patients, SRR was not attempted due to the following causes: Spontaneous cardioversion (36%), Physician's rejection (13%) and disability (3.5%) Only one patient rejects the procedure. Cardioversion-attempted patients were significantly younger (51% of patients >75y. vs. 80%) and had a higher heart rate(12% of patients<100 bpm vs. 36%, p<0.01). There were no significant differences between the two groups when previous antiarrhythmic therapy, structural cardiopathy or current heart failure were analysed. SRR related variables: hemodynamic compromise (OR= 6.3, CI 95%: 1.13 - 35.5), sex (male: OR= 1.98 CI 95%: 1.034 - 3.79), advanced age (OR=0.95, CI 0.93-0.98) and a higher heart rate (OR=1.02). SRR strategies were pharmacological in 88% of cases(success rate of 79%) and electrical(direct-current) in 5%(response rate 85%, no complications recorded).Most used drugs were amiodarone(43% of cases),flecainide(26%) and propafenone(18%).
Conclusions: 1) SRR is not attempted in the ED in most of eligible patients, despite the high success rate observed. 2) DC cardioversion in the ED remains anecdotical, although its efficacy and safety is clearly superior. 3) Most used antiarrhythmics are amiodarone and Ic-class drugs. 4) Hemodynamic instability is the main determinant of cardioversion in the ED. 5) A young man with paroxysmal AF has more likelihood to be cardioverted in the ED than a woman or an old man in the same situation. Factors as hypertension or stroke have no influence on the decision of SRR.

P3456 Verapamil in prevention of early recurrences of atrial fibrillation. Final results of the VERAF study

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Background: Atrial electrical remodeling caused by rate-induced intracellular calcium overload is one of the causes that produce early recurrences of atrial fibrillation (AF)after resumption of sinus rhythmn (SR). Calcium antagonists could theoretically limit atrial remodeling thus leading to a better outcome after cardioversion.
Aim of this prospective, multicenter, randomized study was to evaluate the effect of verapamil (VER) on efficacy of electrical cardioversion (EC) of persistent AF and on incidence of arrhythmia relapse.
Methods: Two hundred-fourteen patients (pts) (mean age 68±9 years) with persistent AF (mean arrhythmia duration 154±105 days), NYHA functional class I-II, left ventricular ejection fraction > 0.40 (mean value 0.55±0.07), were randomized to receive standard therapy (STD) (N=108) or STD + VER 80 mg t.i.d. (N=106), associated to anticoagulation, 3 weeks before and 4 weeks after EC (4 pts were excluded from the study). No additional antiarrhythmic drugs were given. In 6 (6%) pts in VER group, and in 47 (44%) pts in STD, additional digoxin (DIG) was given to control ventricular rate (p<0.0001). We considered end-point of the study the reversion to SR before EC, the inability to stop AF (EC Failure), early relapse of AF within 7 day after EC (ERAF), late relapse between 8-30 days after EC (LRAF), and the persistence of SR 1 month after EC (SR).

	Reversion SR	EC failure	ERAF	LRAF	SR
VER	20/103 (19%)	11/83 (13%)	19/72 (26%)	7/72 (10%)	46/72 (64%)
STD	10/107 (9%)	13/97 (13%)	51/84 (61%)	9/84 (11%)	24/84 (29%)
p value	0.059	NS	<0.0001	NS	<0.001

Results: The two groups were comparable in terms of the mean clinical variables considered. The result are reported in the table.
Immediate recurrence (within 1 hour) were lower in VER group compared to STD group (3/72 pts, 4% vs 18/84 pts, 21%; p=0.004). There was no difference between pts who were taken or not DIG in STD group. VER regimen was 40 t.i.d. in 14/106 pts (13%) pts because of dyspnea (5 pts), bradycardia (4 pts), fatigue (5 pts).
Conclusion: Stand alone VER around EC is effective in reducing early recurrence of AF. The effect is maximum for immediate recurrence reduction. Concomitant use of DIG in pts not treated with VER does not interfere with EC outcome.

P3457 The effect of exercise to P-wave dispersion and its evaluation as a predictor of atrial fibrillation

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Prolongation of p wave time and increase of its dispersion is an independent predictor of paroxysmal atrial fibrillation. In patients (pts) with paroxysmal atrial fibrillation (PAF), as in healthy people, exercise augment sympathetic activity and therefore cause the development of atrial fibrillation. The aim of this study was to evaluate the effect of exercise to p wave dispersion and to predict the development of atrial fibrillation.
Methods: 198 pts (93 women, 105 men; 59±11 years) having the diagnosis of PAF were included in the study. The left atrial diameter of all these pts was more than 4 cm. 155 pts (72 women, 83 men, 58.8±10.8 years), with left atrial diameter more than 4 cm and without PAF were taken as control group. Symptom limited exercise test with modified Bruce protocol was applied to all pts. Rest, maximum exercise and end exercise 1, 3 and 5 minutes 12 derivations ECG was taken in all pts.The velocity of ECG was adjusted to 50 mm/sec; shortest and largest p wave durations were measured and p wave dispersion was calculated.
Results: 6 of 198 PAF pts with AF with exercise were excluded from the study. The mean left atrial diameter was 4.41±0.58 cm in PAF pts and 4.38±0.48 in control group. No differences were found between PAF pts and the controls in exercise time (10.4 ± 3 vs 11 ± 2.7 min); METs (7 ± 1.7 vs 7.3 ± 1.7); resting HR (79 ± 15 vs 80 ± 10 bpm); peak HR (147 ± 23 vs 147 ± 16 bpm); recovery 1 HR (126 ± 19 vs 128 ± 13 bpm); recovery 3 HR (109 ± 16 vs 108 ± 10 bpm); recovery 5 HR (88 ± 12 vs 86 ± 9 bpm). The differences in p wave dispersions with exercise were shown in table.

Differences in p wave dispersion

	PAF pts (n=198)	Controls (n=155)	p value
Resting p dispersion (msec)	75 ± 30	52 ± 20	0.001
Peak p dispersion (msec)	69 ± 12	53 ± 23	0.001
Recovery 1 p dispersion (msec)	69 ± 16	45 ± 20	0.001
Recovery 3 p dispertion (msec)	76 ± 26	54 ± 20	0.001
Recovery 5 p dispertion (msec)	70 ± 26	55 ± 25	0.001

Conclusion: In PAF pts p wave dispersion is significantly longer in rest, maximum exercise and recovery time.

P3458 Atrial fibrillation occurrence after radiofrequency catheter ablation of atrial flutter. Results from the Venetian multicentric study

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Background: Atrial flutter (AFL) and atrial fibrillation (AF) frequently coexist in clinical practice. Both arrhythmias may share the same underlying pathology. Thus, elimination of AFL might not prevent the occurrence of AF during long-term follow-up. Aim of this prospective multicentric study was to evaluate the time to onset of AF during a long-term follow-up in a large cohort of patients (pts) with typical AFL treated with transisthmic radiofrequency catheter ablation (RCA).
Methods: We evaluated 383 pts (75% male, mean age 61.7±11.1 years) who underwent RCA for paroxysmal (52%) or persistent/permanent (48%) AFL. In 239 pts (62%) AF was present before RCA: 34% of these pts had predominantly AF. In 124 patients (32%) class IC drugs (propafenone and flecainide) or amiodarone converted AF into AFL.An underlying structural heart disease was present in 182 pts (48%). The mean left atrial diameter was 43±6 mm, and the mean left ventricular ejection fraction was 59±10%. RCA was performed using a combined anatomic and electrophysiological approach. The target of ablation was the creation of a bi-directional transisthmic block. After ablation, pts underwent outpatient examination after 1 month, and thereafter each 6 months. During follow-up, the incidence of AF was evaluated after 6, 12, 24, 36, and 48 months.
Results: Bi-directional transisthmic block was obtained in 367 pts (96%). Complications were observed in 6 pts (1.6%), including 2 permanent AV block (0.5%). During a mean follow-up of 20.5±12.4 months, relapse of AFL was recorded in 41 pts (11%): 31 pts underwent another successful RCA. Three pts (0.8%) died. At the end of follow-up, 33% of pts with a successful RCA referred AF: paroxysmal in 20%, persistent or permanent in 13%. The incidence of AF increased continuously during the follow-up: AF was present in 24% after 6 months, in 36% after 12 months, in 42% after 24 months, in 52% after 36 months, and in 48% after 48 months.
Conclusions: RCA of AFL is successful and safe. It is useful in pts with coexisting AF, too. However, the evolution of the atrial electrical disease implies that during long-term follow-up AF will occur in a large number of pts.

P3459 Effect of slow pathway ablation/modification on the fast pathway properties in patients with atrioventricular nodal reentrant tachycardia

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Radiofrequency (RF) catheter ablation of the slow pathway (SP) is considered as the treatment of choice for definitive cure of atrioventricular nodal reentrant tachycardia (AVNRT). Modification of AV node conduction by RF current application in the perinodal tissue has been rarely systematically analysed or reported. This study was performed to assess the effect of RF ablation or modification of the SP on the fast pathway properties in a large cohort of unselected patients (pts).
Methods: 223 consecutive pts (149 female; 74 male; mean age 51 ± 16 yrs; heart disease in 28/223) submitted to RF ablation for AVNRT were included in this study. SP ablation was anatomically and electrophysiologically guided using conventional techniques.
Results: Success (defined as AVNRT noninducibility at the end of the procedure) was obtained in 221/223 cases (99%) with a median of 5 RF applications. Complete SP ablation was observed in 96/223 (43%) and SP modification in 127/223 (57%) cases. RF application in the SP region resulted in a significant shortening of the effective refractory period (ERP) of the fast pathway (293 ± 58 ms after RF vs 327 ± 64 ms before RF, $p<0.0001$). Such an effect was observed in the subgroup of pts with SP modification (292 ± 60 ms vs 329 ± 63 ms, $p<0.0001$) and in the subgroup of pts with SP ablation (294 ± 57 ms vs 325 ± 65 ms, $p<0.0001$). Maximal 1:1 AV conduction was also significantly influenced by RF application in the SP region (174 ± 27 bpm before RF vs 171 ± 25 bpm after RF, $p<0.001$) whereas AH interval was not (78 ± 20 ms vs 78 ± 21 ms, $p=0.92$).
Conclusion: In pts with AVNRT, a significant shortening of the ERP of the fast pathway is observed after RF application in the region of the SP and this effect is present both in patients with SP ablation and in patients with SP modification. Further studies are needed to elucidate the mechanisms underlying this observation (vagal withdrawal? modification of electronic influences?).

P3460 Focal atrial fibrillation arising from persistent superior vena cava: mapping and radiofrequency ablation

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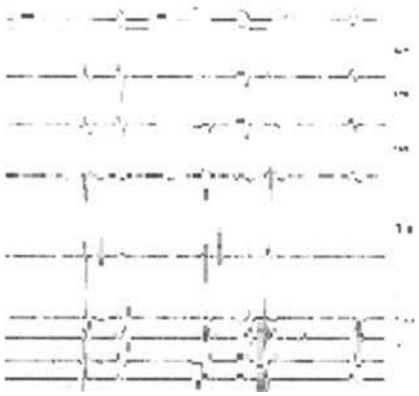
Focal atrial fibrillation (AF) can be initiated by premature atrial contractions (PACs) from pulmonary veins (PVs) and less frequently from superior vena cava, crista terminalis and ligament of Marshall (LOM). RF ablation of focal AF originating from persistent left superior vena cava (LSVC) has never been described. We report the case of a pt who underwent EPS for episodes of paroxysmal AF unresponsive to AA drugs. The pt had a persistent LSVC inserting in the posterolateral CS. The rhythm was sinus (SR) interrupted by frequent PACs that initiated episodes of AF. Double potentials were recorded in persistent LSVC close to insertion in CS (Fig 1, LSPV: left superior PV). In SR, an initial far-field atrial component is followed by a late sharper LSVC component, whereas during PACs the sharp potential is preceding the atrial component indicating that LVSC was the site of PACs origin. Two RF applications caused the disappearance of PACs and of LSVC potential. During follow-up (12 mos), the pt was free of PACs and episodes of AF without AA drugs.



Conclusions: we describe the unique case of successful ablation of focal AF arising from persistent LSVC. The involvement of this structure in triggering AF is not surprising, as the LOM, a common site of origin of focal AF, is the embryological remnant of LSVC.

P3461 How reliable are symptoms for detection of atrial fibrillation in clinical routine? Results of the PAFAC trial

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The PAFAC Trial (Prevention of Atrial Fibrillation After Cardioversion) is a prospective, double-blind, randomized, placebo-controlled study. In 39 months, 1,182 pts. showing documented chronic atrial fibrillation (AF) were included in 99 centers in Germany and in the Czech Republic. After successful cardioversion, 848 pts. could be randomized to either sotalol, quinidine + verapamil or placebo. Endpoints were either documented AF recurrence or death of any kind. All pts. were followed until an endpoint occurred or the end of the trial was reached. The mean follow-up period was 249 ± 315 days. All pts. received a personal small ECG recorder (Tele ECG) and were asked to record and transmit via telephone at least 1 ECG per day during the total follow-up. All ECGs were immediately analyzed in a central unit. Only AF recurrences documented by ECG were assumed as valid, independent of related symptoms. In case of AF, a fax was sent immediately to the investigator, initiating an extraordinary visit of the pt. Subsequently, a Holter recording was performed to discriminate between paroxysmal and chronic AF. In addition, the pt. was asked for associated symptoms (irregular heart beats, dizziness, tachycardias, syncopes) at the time of primary AF recording.

A total of 191,103 Tele ECGs were recorded and transmitted, of which 95% were valid for complete analysis. In 572 pts. (67%) at least 1 episode of AF was documented,in 352 pts. (42%) AF was subsequently defined as chronic. Irregular heart beats occurred in 23%, dizziness in 7%, tachycardias in 13% and syncopes in <1% of all documented AF episodes. Altogether, 70% of documented AF recurrences occurred completely asymptomatic and have occasionally been detected by daily Tele ECG monitoring. There is a tendency towards higher rates of symptomatic episodes in case of paroxysmal AF. The data suggest a correlation between higher heart rates and the occurrence of symptoms, only.

With respect to these findings it is questionable, whether associated symptoms are still valid parameters for a reliable detection of AF in clinical routine, especially if they are the basis of decisions for therapeutic strategies (e. g. immediate cardioversion without anticoagulation).

P3462 Flecainide but not sotalol causes post-repolarization refractoriness in the fibrillating atrium of patients with long-lasting atrial fibrillation

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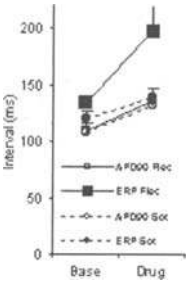
Potassium and sodium channel blockers may terminate atrial fibrillation (AFib) and prevent its reinitiation after cardioversion. In addition to prolonging action potential duration (APD), sodium channel blockers may induce post-repolarization refractoriness (PRR). Whether these drug effects are present in the fibrillating atrium is not known. We thus studied the effects of Flecainide (Flec) and Sotalol (Sot) in the fibrillating human atrium.

[Image] In 12 patients with persistent AFib (11male, 58 ±17 yrs, 27±24 mo duration of AFib), we simultaneously recorded monophasic action potentials (MAP) from the right atrial appendage and septal right atrium at baseline and 15 minutes after IV administration of Sot (1.5mg/kg) or Flec (2 mg/kg). Effective refractory periods (ERP) were determined by delivering extra stimuli at increasing coupling intervals (5ms steps) until local capture was reproducibly documented. APD was measured at 70% (APD70) and 90% (APD90) repolarization. PRR was calculated as ERP-APD90.

Flec and Sot both prolonged APD (APD70: Flec 110 ±7 vs 88 ± ms*, Sot 106 ± 6 vs 88 ± 6 ms*; APD90: Sot 131 ± 8 vs 108 ±6 ms*, Flec 137 ± 10 vs 109 ± 7 ms*, *p < 0.05). Sot prolonged ERP slightly more than APD (ERP: 119 ± 8 vs 139 ± 8 ms*), whereas Flec induced marked PRR (mean 54 ms*, ERP: 133 ± 6 vs 197 ± 22 ms*, figure).

Conclusions: Sot and Flec prolong APD in the fibrillating human atrium. Flec but not Sot also induces PRR. Both of these effects contribute to wave length prolongation. PRR may explain the effectiveness of Flec to prevent reinitiation of AFib after cardioversion.



Effect of Sot and Flec on APD and ERP.

P3463 Bisoprolol and sotalol in treatment of recurrent atrial fibrillation in patients with coronary artery disease. Bisoprolol is beyond comparison

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To compare long- and short-term efficacy and safety of bisoprolol (B) and sotalol (S) in maintaining sinus rhythm (SR) in pts with recurrent atrial fibrillation (AF) with documented coronary artery disease (CAD).

Methods: 128 pts (39 female, mean age 57± 12 yrs) with recurrent AF, 60 were given S and 68 B, after restoration of (SR). Pts randomized to S began with 80 mg twice daily and B 5 mg once daily. The dose was individually increased to the highest well-tolerated dose. All of them were on standard and similar therapy. The proportion of pts relapsing in AF with/without side effects was calculated for the two groups using the Kaplan-Meier method.

Results: 41 of the 60 (68.3%) pts receiving S relapsed to AF after an average of 7.1±6.5 months, compared to only 8 of the 68 (11.8%) pts given bisoprolol, after an average of 8.3±8.7 months ($p < 0.0003$). 7 pts (all of them on S) experienced side effects necessitating immediately withdrawal of medication, nevertheless 6 of them are still in normal SR. The proportion of AF/side effects free pts at the 1-year follow-up examination in the B group was higher than in S group (34% vs 26%), and 2 years later the results was more than double (29% vs 12%, for B and S respectively).

Conclusions: Long- and short-term efficacy of B is highly superior to S for the maintenance of SR in pts with recurrent AF with CAD and about side effects B is beyond comparison.

P3464 Factors determining long-term maintanace of sinus rhythm after successful cardioversion of persistent atrial fibrillation

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Long term maintenance of sinus rhythm (SR) after successful cardioversion of persistent atrial fibrillation (AF) carries lower risk of stroke and may avoid the risks associated with anticoagulation. We sought to determine the clinical and echocardiographic predictors of maintained SR during one year follow-up period.

Methods: Our study population comprised 219 patients (pts) (F/M 80/139; mean age 61.4±17.6); 109 of them (F/M 35/74; mean age 61.1±7.2) were randomized to SR restoration and maintenance with serial antiarrhythmic drug usage for whom clinical, transthoracic echocardiographic (TTE) and exercise test (ExT) variables were recorded prior to CV. The relation between those variables and SR maintenance at one year was examined. Generalized additive logistic regression was used to investigate impact of selected variables on long-term SR maintenance. Variables of interest were age, gender, echo parameters such as long, short axis of LA, LA and RA area, shortening fraction and LV end diastolic diameter, time of atrial fibrillation duration NYHA functional class and concomitant diseases. Binary variables (gender and sex) were represented in model as dummies. Impact of other parameters on long term SR maintenance and significance of its non-linear shape was tested. For parameters in which non-linearity of association was not significant relative risk associated with one unit of this variable increase was computed. For non-linear parameters, after inspection of plot of its dependence was linear selected. Than regression was performed on data from this intervals and specific for this interval relative risks associated with one unit of analyzed variable increase were computed.

Results: SR was presented in 64.4% pts at one year. For quantities variables series of generalized additive logistic regression models with one parameter of interest adjusted for age and sex was fitted. Linearity of dependence of echocardiographic and ExT parameter of interest with ID success was tested. Increased left atrium area >28 cm^2; $p<0.04$; RR 1.64 (1.12-2.64), and increase of FS value in ranges between 26-40%; $p<0.003$; RR 1.31 (1.06-1.72), were significantly associated with SR maintenance after 12 months observation period.

Conclusion: Among all considered variables only left atrium area and shortening fraction seem to be good predictors of SR maintenance after successful CV of persistent AF in one year follow-up.

P3465 Effects of diltiazem and esmolol on cycle length and spontaneous conversion of atrial fibrillation

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Background: Patients with atrial fibrillation (AF) frequently receive calcium channel blockers (CCB) for ventricular rate control. There is evidence that CCB also exert direct effects on the atrium and prolong the duration of AF. Esmolol (Esmo) is not known to have any direct effects on the atrium. The purpose of this study was to compare the acute effects of intravenous diltiazem (Dilt) and Esmo on the cycle length (CL) and conversion rate of pacing-induced AF.
Methods and Results: In 41 adults without structural heart disease (13 male, age 44±17 years, LVEF 0.6±0.03) AF was induced by rapid atrial pacing. After 3 mins, pts were randomized to to receive either i.v. Dilt 0.25 mg/kg i.v. over 2 mins followed by a 1.7 mg/min infusion over 13 mins (n=13), i.v. Esmo 500μg/kg followed by 50-200 μg/kg/min over 14 mins (n=15), or 0.3 ml/kg saline (Plac, n=11). If AF converted spontaneously within 8 mins, AF was reinduced. AF persisting for >15 mins was cardioverted electrically. After 8 mins, the AF-CL shortened to a significantly higher degree in the Dilt group than in the Esmo group or the Plac group (table). At the same time, the ventricular CL prolonged significantly in the Dilt group (523±115 ms vs 850±214 ms, P<0.001) and the Esmo group (508±86 ms vs 571±79 ms, P<0.001). Spontaneous termination of AF occurred significantly less often in the Dilt group (3/13 pts, 23%) than in the Esmo group (10/15 pts, 67%, P<0,05) and the Plac group (10/13 pts, 77%, P<0.01).

Table: Changes in AF-CL (ms)

	Dilt	Esmo	Plac
Minute 1	183±19	169±28	189±35
Minute 8	140±19*	165±24	173±37
P	0.001	0.6	0.005

*P<0.05 vs Plac

Conclusion: Dilt, but not Esmo, shortens the AF-CL and lowers the probability of spontaneous conversion of recent-onset AF to sinus rhythm. These suggests that the use of diltiazem for acute rate control may unwittingly prolong the duration of recent-onset AF.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR – CLINICAL AND TECHNICAL ASPECTS

P3466 Effects of implantable cardioverter-defibrillator therapy on survival in chronic heart failure patients awaiting for transplantation

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The impact on survival of ICD therapy has been evaluated in 506 CHF patients (pts) awaiting heart transplantation (HXT) from 1992 to 2001. Fifty-one pts (92% male) were implanted because of ventricular fibrillation (VF) (n=34) or sustained ventricular tachycardia (SVT) (n=17). Age and LVEF were similar between pts with and without ICD (51±10 vs 53±10 yrs, 24±9 vs 25±6%) while NYHA class and wedge pressure were significantly lower in ICD patients (2.5±0.6 vs 2.9±0.7, 17±8 vs 22±9 mmHg, p<0.01). During a mean follow-up of 18 months (range 0.13-118) 33 ICD patients were appropriately shocked for fast VF or VF. Ten patients (20%) died for heart failure or were urgently transplanted including 6 who were previously shocked. Death for heart failure or urgent HXT occurred in 151 no-ICD patients (33%) and sudden presumably arrhythmic death in 52 (11%). In no-ICD pts those with arrhythmic deaths could not be identified based on traditional risk factors. Survival curves for total cardiac mortality are displayed below for: A) ICD patients, B) no-ICD patients, C) ICD patients censored at the time of the first appropriate shock.
Conclusion: These data suggest that ICD, in a high risk CHF population, markedly improves both survival and the chance of receiving HXT. Risk stratification is needed to select those CHF pts who may benefit most from primary prevention with ICD.

P3467 Heart rate turbulence in patients with implanted cardioverter-defibrillators

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Background: Heart rate turbulence, reflecting baroreflex sensitivity, has recently been described as predictor of cardiac events in postinfarction patients. The aim of this study was to determine prognostic significance of heart rate turbulence in patients with implantable cardioverter-defibrillators (ICDs).
Methods: In 63 high-risk patients with decreased left ventricular function and ICDs, a short-term (10-minute) high-resolution ECG recording was performed after which patients were followed for 25 months on average with cardiac death as primary endpoint and ICD shock or cardiac death as secondary endpoint. Heart rate turbulence was evaluated using turbulence slope and turbulence onset parameters computed in 29 of those patients who presented with at least on premature beat during 10-minute ECG.
Results: During 25-month follow-up, cardiac death occurred in 9 (31%) whereas ICD shock or cardiac death occurred in 15 (52%) of 29 patients. The turbulence slope was significantly smaller in patients with than without cardiac death (0.049±0.038 vs. 0.116±0.081, respectively; p=0.034), whereas turbulence onset did not differ significantly between two groups. None of heart rate turbulence parameters was significantly different when comparing patients with and without secondary endpoints.

HRT and Outcome in ICD Patients

	Alive (n=20)	Death (n=9)	p value
Ts (ms/RR)	0.116±0.081	0.049±0.038	0.034
To (%)	-0.003±0.039	0.004±0.012	0.378
	Event-free (n=14)	Cardiac Death or ICD Shock (n=15)	
Ts (ms/RR)	0.104±0.072	0.090±0.080	0.534
To (%)	0.004±0.038	-0.004±0.029	0.896

Values in parentheses are standard deviations

Conclusions: These observations indicate that heart rate turbulence slope is predictive for cardiac death in ICD patients with left ventricular dysfunction. However, lack of significant association between heart rate turbulence and secondary endpoints may suggest that compromised baroreflex sensitivity may indicate increased risk of non-arrhythmic cardiac events.

P3468 Primary prevention of sudden cardiac death following myocardial infarction: how many patients are candidates for an implantable cardioverter-defibrillator?

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Prophylactic implantation of an ICD improves survival in high risk pts. with remote MI. The MADIT trial showed a significant benefit for pts. late after MI with poor ejection fraction (EF), nonsustained ventricular tachycardia (nsVT) on Holter ECG and inducible but not drug-suppressible sustained VT. Recently presented results indicate that pts. with low EF alone (<=30%) late after MI benefit from a prophylactic ICD. Other primary prevention trials are on its way also studying high risk pts. early after acute MI. We showed in a previous study that only a very small group of pts. with remote MI (0.2%) fulfills the strict MADIT criteria. However, the portion of potential ICD-candidates in unselected groups of post MI pts according to the proposed criteria is unknown.
Method: We applied various noninvasive criteria as used in the different primary prevention trials to a consecutive series of 790 post MI pts. <75 years (males 76%, mean age 59±10 yrs.) from our MI data base. Medical history: previous MI 17%, diabetes mellitus 19%, arterial hypertension 46%, smoker 57%. Clinical data: anterior MI 45%, transmural MI 80%, thrombolytic therapy 59%, PTCA 39%, ACVB 11%. Risk stratification was performed by EF and Holter ECG prior to discharge (10±6 days after MI). Risk groups were defined according to the following criteria: EF<=35% + nonsustained ventricular tachycardia (nsVT) on Holter ECG, EF<=30%, EF<=35% + mean HR>=80/min on Holter, and nsVT>=150/min on Holter.
Results: Using EF<30 the number of ICD candidates within the post MI population was as high as 18.4% (145/790). Under application of EF<35+HR>80 we found 10% (79/790) ICD candidates. Combining EF<35 with nsVT revealed a group of 4.4% (35/790). If selection was done by nsVT>150 3.5% (28/790) fulfilled this criterion.
Conclusion: The results of primary prevention trials in post MI pts. will substantially increase indications for prophylactic ICDs. However, the increase highly dependends on the criteria used.

P3469 The use of Implantable cardioverter-defibrillators in patients with hypertrophic and arrhythmogenic right ventricular cardiomyopathy. A large national database

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Background: Non randomized multicenter studies have demonstrated the usefulness of ICD treatment in particular subgroups of patients with hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD). The large application of those studies and the guidelines on the ICD use are not well known.
Aim: To assess the implant rate of ICD in patients with well-defined diagnosis of HCM and ARVD in the 58 million Italian population and to compare the main epidemiological data and clinical characteristics of the two groups.
Methods: All the data were collocated by EURID forms in the Italian ICD Registry. The study population included all the patients treated by ICD between 01-07-1997 and 31-12-2000.
Results:

	HCM	ARVD	p
Estimated Prevalence	1:500	1:1000-10.000	N.S.
N° implants (% on the overall)	156 (29%)	127 (2.35%)	N.S.
Centers (% on the overall)	80 (30.42%)	63 (23.96%)	N.S.
Average age	56	48	N.S.
Male	115 (74%)	96 (76%)	N.S.
NYHA Class I-II	123 (79%)	109 (86%)	N.S.
LVEF >50	71 (46%)	68 (54%)	N.S.
Amiodarone	54 (34%)	44 (34%)	N.S.
Ventricular Tachycardia	85 (35%)	92 (72%)	0.003
Ventricular Fibrillation	49 (32%)	20 (15.7%)	0.004
VT and VF	5 (3%)	11 (8%)	N.S.
Syncope/Presyncope	82 (53%)	57 (45%)	N.S.
Cardiac Arrest	30 (19%)	17 (13%)	N.S.
Palpitations/ Other	33 (21%)	48 (38%)	0.017
Prophylactic ICD	10 (7%)	5 (4%)	N.S.

Conclusion: The ICD implant rate in patients with HCM and ARVC appears still limited in a large single country of European population considering the prevalence of the two syndrome. About 1/3 of the Italian centers are involved in this activity. Ventricular fibrillation is the main indication in patients with HCM, while ventricular tachycardia is more frequent in ARVC. The prophylactic ICD use concerns less than 10% of cases.

P3470 Incidence of spontaneous atrial and ventricular tachyarrhythmias in patients with a defibrillator and a history of atrial tachyarrhythmias

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The aim of the prospective study was to evaluate the incidence of spontaneous atrial and ventricular tachyarrhythmias in patients with a history of spontaneous atrial and ventricular tachyarrhythmia. Inclusion criteria were a standard indication for the implantation of a cardioverter defibrillator (ICD) and at least one documented spontaneous atrial tachyarrhythmia within the last year.
Methods: Patients received the dual-chamber ICD VENTAK PRIZM AVT (Guidant). The device has new algorithms that differentiate atrial flutter from atrial fibrillation, have separate therapy options for the treatment of atrial flutter and atrial fibrillation (Antitachycardia Pacing (ATP) and/or shock therapy), and have diagnostic functions that allow a selective storage of spontaneous atrial and ventricular tachyarrhythmias (16 min with intracardiac electrograms and annotated event markers).
Results: The study included 84 patients in 22 European and one Canadian center (64 ± 13 years, male n = 62, coronary artery disease n = 49, LVEF 45 ± 15%). Paroxysmal atrial tachyarrhythmias in combination with monomorphic ventricular tachycardia had 56 patients, paroxysmal atrial tachyarrhythmias and ventricular fibrillation 21 patients and 7 devices were implanted for paroxysmal atrial tachyarrhythmias only. Follow-ups were at predischarge, 1,3 and 6 months after implantation. During a cumulative implanted duration of 503 months the device documented 5717 spontaneous atrial episodes in 58 (69%) patients and 2630 spontaneous ventricular episodes in 45 (53%) patients. Both atrial and ventricular spontaneous episodes during a mean follow-up duration of 2.1 months had 32 (38%) patients. The spontaneous atrial tachyarrhythmias were successfully terminated by ATP in 1602 episodes and by shock therapy in 44 episodes. The remaining episodes terminated spontaneously. Of the spontaneous ventricular episodes, 305 were successfully terminated by ATP and 201 by shock therapy. The remaining episodes terminated spontaneously.
Conclusions: Patients who receive an implantable defibrillator and with a history of atrial tachyarrhythmias have a high incidence of spontaneously atrial tachyarrhythmias after device implantation. These patients are also at high risk of suffering from ventricular arrhythmias (38%). Spontaneous atrial tachyarrhythmias can be successfully diagnosed and treated with ICD's that offer options to selectively detect and treat atrial tacharrhythmias.

P3471 Comparison between automatic nocturnal and manual shocks in patients with drug refractory atrial fibrillation treated with a dual defibrillator

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Background: The Medtronic 7250 is an implantable atrial (dual) defibrillator (ICD) with multiple programmable therapies options. Ventricular therapies back up allows programming the atrial shocks in an automatic fashion. The differences of this automatic strategy with manual one are unknown.
Aim: The aim of the study has been to evaluate whether there are long term differences with automatic or manual shocks in the atrial fibrillation (AF) temporal course and clinical status of ptes with dual ICD for refractory AF.
Methods: 40 Pts (28 M, mean age 65±10)with symptomatic, drug refractory AF (60% persistent, 40% paroxismal) received a Medtronic 7250 ICD. Preventing and antitachycardia pacing therapies were activated. 14 (35%, group A) pts accepted automatic shock therapy, programmed as 1 single, over night, maximal energy (27 J) shock by episode. In the other 26 ptes (65%, group B)device shocks were delivered by a physician in the hospital. AF burden (AF hours by week), number of episodes, efficacy, ERAF, tolerability, symptoms and QoL data has been evaluated to study the impact of the automatic shocks. All patients completed 1 year of follow-up.
Results: In both groups, dual ICD decreased AF burden, number and duration episodes. However during some periods significant differences in AF burden were found due to longer duration of AF episodes in group B.Tolerability of automatic shocks was high with only one patient needing a temporal interruption, and was related to the success of the therapy and mainly with the rate of the shocks
Conclusion: Automatic shocks seem reduced more effectively AF burden during burden.Tolerance is good when they are delivered as only 1 shock during nightime.

P3472 Do implantable cardioverter-defibrillator patients really live longer? A reassessment after 10 years

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Background: In 1993, we published the results of 107 patients (pts.) treated with an ICD in combination with endocardial defibrillation leads (Böcker et al, JACC 1993). The purpose of this study was to investigate the long-term follow-up (FU) of these patients.
Patients and Methods: The follow-up of 107 pts. (86% male; 68% CAD, 17% DCM; EF 40%±15; VF 29%, sustained VT 50%, VT and VF 18%), implanted between October 1989 and March 1992, was studied 10 years after ICD implantation (November 2001).
Results: After a follow-up of about 10 years, 54 pts. (50%) out of the 107 are still alive. 4 pts. (3,74%) underwent heart transplantation (mean 61,1 months after first ICD implantation), of whom 3 are still alive.
Death occurred after a mean of 56 months (median 54± 36). Cause of death was sudden in 6 pts. (9% of all deaths) after 62±35 months and progressive pump failure in 28 pts. (53%) after 53±34 months. Thirteen pts. (25%) died from a non cardiac cause. The cause of death remained unknown in 2. Three pts. died within 30 days after first ICD implantation, 2 of them after failed implantation of an endocardial lead system.
Thirty-four pts. (33%) had VF or fast VT >240 bpm, 84 pts. (81%) sustained VT. However, 19% of the pts. had neither VF nor VT-episodes. Inappropriate ICD therapies occurred in 34 pts. (33%), the majority of which were caused by atrial fibrillation with fast AV-conduction.
Lead-related problems requiring repeated surgery were a common finding, occurring once in 50% of the patients and more than once in 10%. The majority of the lead problems included the Pacing/sensing part of the lead, followed by insulation problems and infections. The high-voltage circuit was included only in a minority of the patients. Only 2 pts. had a dysfunction of the ICD itself.
Conclusions: ICD treatment reduces the sudden death rate even during long-term follow-up to .5%/year and, thus, improves the prognosis of the treated patients. Progression of pump failure is the leading cause of death in this patient cohort. The incidence of lead dysfunction requiring repeated surgery is high while dysfunctions of the device itself are a rare finding.

P3473 Syncope in implantable cardioverter-defibrillator pacemaker dependent patients

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Background: With the current Automatic Gain Control (AGC) implantable cardioversor defibrillators (ICDs), maximum sensitivity is programmed to guarantee ventricular fibrillation detection. Ventricular oversensing may allow inappropriate tachyarrhythmia detections and therapy and pacing inhibition. The incidence of ventricular oversensing is unknown. Its consequences in pacemaker dependent patients are dangerous. **Objectives:** To evaluate ventricular oversensing frequency in pacemaker dependent patients, with AGC ICDs implanted. **Population:** We studied 8 ICD pacemaker dependent patients (P), (4.8% of all AGC ICDs implanted in our department). Six P had a dual chamber ICD (3 with ventricular resynchronisation) and 2 P single chamber ICDs. **Results:** Four P suffered (at least 1) syncope in follow up, and one died suddenly, corresponding to 63% of P with serious complications. The device interrogation in these patients showed: oversensing episodes (false detection of VF) followed by pacing inhibition and shock - 3 P; absence of arrhythmia detection - 2 P. The P that died (dual chamber ICD with resynchronisation) was among the latter (the autopsy excluded lead dislodgment and was not conclusive as to the cause of death) **Conclusions:** Oversensing in this population seems frequent and may constitute a high potential risk. Precautions should be taken as to the choice of the device in pacemaker-dependent patients. Better sensing systems, eventually with tachy and brady independent sensing may pssibly contribute to solve these problems.

P3474 Reliability and clinical benefits of a new subthreshold non-invasive shock lead integrity test

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The integrity of the defibrillation lead is crucial for the proper function of implanted cardioverter/defibrillators. Serial measurements of the shock lead impedance are the most reliable non-invasive method to verify the integrity. The current approach is to deliver an at least 1 J shock. As this is painful for the patient, deep sedation is mandatory. The aim of the prospective study was to compare a new subthreshold measurement for shock lead impedance with the standard measurement. **Methods:** The study included 123 patients (60±13 years, 82% male, 71% coronary artery disease, ejection fraction 38±16%) who received in 25 European centers either a Prizm DR (n=73) or VR (n=50, Guidant, St. Paul, MN, USA) defibrillator. The defibrillator was connected to the single coil (models 0127/0128; n = 39) or dual coil (models 0147/0148; n = 84) Endotak Reliance defibrillation lead. The defibrillator delivers for the shock lead integrity test a <1 mJ subthreshold pulse through the single coil or dual coil lead and the defibrillator housing (can). The current density of the test pulse is 1/100th of a pacing pulse. Non-invasive shock lead impedance was measured for the defibrillation vectors from the distal coil to the proximal coil and can as well as from the distal coil to the can. The standard measurement for shock lead impedance was with a 17J shock. **Results:** The shock lead impedance for the vector from the distal coil to the proximal coil and the can was 42 ± 5 ohms (95% confidence interval (CI): 41 - 44 ohms) with the lead integrity test and and 41 ± 4 ohms (±95% CI: 39 - 43 ohms) with a high-energy shock (p = 0.13).The shock lead impedance for the vector from the distal coil to the can was 63 ± 7 ohms (±95% CI: 60 - 66) with the lead integrity test and 60 ± 8 ohms (±95% CI: 56 - 64 ohms) with a high-energy shock (p = 0.44). The vector from the distal coil to the can had a significant higher shock lead impedance than from the distal coil to the proximal coil and the can (p=0.001). **Conclusions:** The new subthreshold shock lead integrity test measured a shock lead impedance similar to the standard measurement with the delivery of the high-energy shock. This non-invasive test is a useful diagnostic method as it allows serial measurements of the shock lead impedance during follow-up without the need for sedation.

P3475 Chronic values of shocking lead impedance compared to impedances at implant – Results of the LIT study

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Background: To test the integrity of the shocking lead a shock must be delivered. Low energy sub threshold test shocks allow to evaluate the shock lead integrity, without being painful to the patient. In the present study we evaluated the Lead Integrity Test (LIT) in VENTAK PRIZM I and II ICDs (Guidant, St. Paul, MN, USA) at implant and during follow-up.

Method: 132 Patients (81,1% male, mean age 61.1 ± 13.8 years, LVEF 43.6 ± 16.1%) with an ICD indication were included in the study. 113 completed all procedures. At implant the LIT was compared against low energy test shocks. At predischarge (PHD) and after 3 months the lead impedance was evaluated again using the LIT.

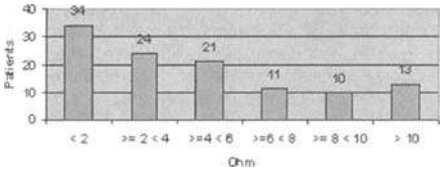
Results: LIT delivers significant lower values than the low energy shock at implant (see table). The acute lead impedance measured at PHD is significantly lower than the impedance measured at implant ($p < 0.0001$). The chronic impedances are not significantly higher than the impedances at implant.

Impedance values

	Implantation	Predischarge	3-months - Follow-up
1.1 J ICD - shock	54.1 ± 13.7 Ohm		
LIT	50.0 ± 12.3 Ohm p < 0.009	46.1 ± 9.9 Ohm	51.2 ± 11.7 Ohm

Values as mean ± standard deviation

The median difference between the impedance at implant and the chronic impedance value is 3.8 Ohm (see picture).



Difference from implant value at 3 months follow-up.

Conclusion: The lead integrity test is a useful and reliable tool to verify the proper function of the defibrillation lead and improves patient comfort and tolerance.

P3476 Complete device removal together with reimplantation of a new device is the optimum management of infected pacemaker and implantable cardioverter-defibrillator leads

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Background: Pacemaker and ICD infection is a life-threatening situation. The incidence of infection in these devices ranges from 1.3-12.6%. However optimum management of these infected devices is yet to be defined. Taylor et al, Trinkle et al and Lee et al have emphasized the conservative treatment of infection without total device removal. Our approach has been total removal of the infected device with reimplantation of new device after proper antimicrobial therapy.

Objective: To come up with a standard protocol for the management of infected pacemaker and defibrillator leads.

Method and Results: between 9991-2001,180 consecutive patients with 320 leads satisfied the criteria of device related infection and underwent device explantation. Infection was defined as presence of warmth, erythema, swelling, edema and pain along with positive culture from blood, device, device pocket, or lead.145 patients had pacemaker and 35 patients had ICD's. The study included 130 male and 50 female patients. The mean age of the patients was 66±15 years (range 20-92 years.). Early infection (<6 months) was found in 31% patients and late infection (>6 months) was observed in 69% patients. The mean implant duration was 52 months (range 2- 264 months). Infection was found to be local in 56% patients, systemic in 21% patients, erosion in 18% and vegetation in 9% patients. Infection was caused by Staphylococcus in 82%, Enterobacter 5%, Pseudomonas 5%, Streptococcus 5% and 1% each by Candida, Citrobacter, Corynebacterium, and Propionibacterium. Complete device removal was achieved in 171 (95%) patients. 150 (84%) patients had reimplantation of the new device at the same center after antimicrobial therapy. During follow up of 36 months only two (1%)patients had reinfection of the reimplanted device. The overall complication rater was 4%.

Conclusion: Complete extraction of the infected device followed by an antimicrobial therapy of choice is a safe and effective way of management of these device related infected devices. Reimplantation of the new device could be done after two consecutive r negative cultures and negative TEE. Although our study was non-randomized it provides substantial insight into successful management of infected device in a large population.

P3477 Non-invasive optimization of the atrioventricular delay in patients under biventricular pacing

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Biventricular (BiV) pacing has evolved as a promising add on therapeutic tool in patients with chronic heart failure. In addition to systolic improvement diastolic resynchronisation may be achieved by optimizing the atrioventricular timing.
Methods: 16 patients (ejection fraction 29±6%, end diastolic left ventricular diameter 65±5mm) received a BiV implantable cardioverter defibrillator (Medtronic InSync™). Doppler echocardiographic evaluation of diastolic and systolic flow durations were performed for different atrioventricular (AV) delays (30ms to 150ms) and different stimulation sites (left ventricular (LV), right ventricular (RV) and BiV). The optimal atrioventricular delay for each stimulation site was calculated using the Ritter-Lemke formula.
Results: QRS duration narrowed during BiV pacing from 208±37ms to 169±16ms. The mean optimal AV delay was calculated to be 117±36ms (60 to 180ms) for BiV, 102±30ms (65 to 150ms) for LV and 75±35ms (50 to 125ms) for RV pacing with wide interindividual differences. Optimized BiV pacing produced the shortest pre-ejection intervals (PEP) (150±44ms) and longest ejection duration (EP) (269±35ms) as parameters of improved systolic inter- and intraventricular contractile synchrony compared to LV (PEP 169±35ms, EP 262±35ms) or RV (PEP 182±28ms, EP 256±46ms) pacing. Diastolic right and left cardiac filling times were longest during BiV pacing. Compared to the mean of the non-optimal AV delays diastolic optimization improved preejection and ejection intervals and prolonged diastolic filling duration independent to the stimulation site.
Conclusions: Individual programming of BiV pacing devices for optimizing hemodynamic benefit is needed because of widely differing electro-mechanical delays. Optimization not only improves diastolic ventricular filling but also increases systolic functional parameters. Compared to monoventricular pacing BiV stimulation increases mean EP (+1% versus LV and +3% versus RV pacing) and shortens PEP (-13% versus LV and -22% versus RV). BiV stimulation prolongs mean diastolic left cardiac filling compared to LV (+12%) or RV (+9%) pacing.

P3478 A rhythm discrimination algorithm based on rate-branch and morphology discrimination in dual chamber cardioverter-defibrillators

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Morphology Discrimination (MD) is a discriminator based on QRS morphology analysis implemented in St. Jude Medical dual-chamber implantable cardioverter defibrillators (ICD). In these devices detected events are firstly classified according to atrial (A) and ventricular (V) median rates (Rate Branch); then a series of discriminators,i.e. MD and Stability if V rate < A rate or MD and Sudden Onset if V rate = A rate, analyse the rhythm according to definite criteria and to different diagnostic logic for ventricular tachycardia (VT) diagnosis (i.e. requiring "any" or "all" the specific discriminators indicating VT, respectively). All rhythms are classified as VT if V rate > A rate.
The accuracy of Photon DR diagnostic algorithm was evaluated on 645 detections occurred in 25 patients during a follow-up of 15±4 months.
All the detected events (645 overall) were reviewed and classified as: 79 atrial fibrillation (AF) episodes, 53 atrial tachycardias, 62 atrial flutter, 203 sinus tachycardias, 234 VTs and 14 ventricular fibrillation episodes.
Overall, specificity on 397 supraventricular arrhythmias (SVT) was 73.5% (292/397) with the diagnostic logic "any" and 90.9% (361/397) with the diagnostic logic "all". Sensitivity on VT episodes was 100% and 98.7% (231/234) with "any" and "all", respectively. In detail, with the diagnostic logic "any", specificity was 88.6% for AF, 0% for atrial tachycardia, 40.3% for atrial flutter and. 97.0% for sinus tachycardia. With the diagnostic logic "all" specificity was 92.4% for AF, 54.7% for atrial tachycardia, 93.5% for atrial flutter and 99.0% for sinus tachycardia.
The use of Morphology Discrimination was crucial for improving the specificity of Rate Branch algorithm. (without this discriminator the highest specificity achievable overall was 74.6%).
In conclusion, implementation of Morphology Discrimination in an ICD with atrial and ventricular sensing, in combination with a Rate-Branch classification system, allows attainment of a very high specificity in discriminating detected events, with maintenance of 98.7-100% of sensitivity for ventricular tachyarrhythmias. With this algorithm the advantage in rhythm discrimination is strictly dependant on use of Morphology Discrimination algorithm, since a marked increase in specificity results from addition of this discriminator to the conventional discriminators (i.e. Sudden Onset and Stability). The net increase in specificity is particularly relevant in discrimination of regular supraventricular tachyarrhythmias (i.e. atrial flutter, atrial tachycardias).

P3479 Low incidence of inappropiate shocks in a dual chamber cardioverter defibrillator: an analysis of a cohort of 197 patients

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One of the most frequent reasons for inappropiate shocks in ICD recipients is atrial fibrillation (AF). Therefore the aim of this study was to assess the number and causes of inappropiate shocks in dual-chamber ICD patients. Special attention was paid on all atrial fibrillation episodes and the effect of programming a slow VT-zone.
Methods: A cohort of 197 patients (pts) and their episodes were reviewed (177 males, 64 ± 10 years, left ventricular ejection fraction = 39 ± 16%) implanted with a dual chamber ICD (Defender IV, Alto DR, Ela Medical, France). Fifty-one pts had a previous history of an atrial arrhythmia. All devices were programmed with 2 VT zones starting at 100 bpm and a VF zone. Shock therapy in the slow VT zone was left to the investigator's judgement. All pts had PARAD or PARAD+ detection algorithm programmed. All documented episodes were retrieved from the memory of the device at each follow-up. The investigator and a group of experts when equivocal reconfirmed whether therapy delivery was adequate or inadequate. Results: During a mean follow-up of 5.6 months, 93/197 pts experienced 434 treated episodes. Among those, 95 episodes were treated by shock in 45 pts. Of the 95 episodes 83 were clinical VT of VF in 38 pts. In 9 pts, 12 episodes were inappropriately treated: 6 episodes of ventricular artifacts (5 pts, 3 with lead problemns, 2 with external interference), 2 episodes of T wave oversensing (1 pts) and 2 AF episodes inappropiately classified as VT (2 pts). Among the 233 AF episodes (25 pts) that were not associated with shocks, 25 (8 pts) triggered ATP therapy without deleterious effect. Therapy was appropiately withhold in 208 (88%) of AF episodes.
Clinical Implication: 1. Only 1% of all ICD-recipients and 4% of all shock treatments were caused by misdiagnosis of atrial fibrillation. 2. Inappropiate shocks were mainly related to ventricular lead problems.

P3480 Assessment of defibrillation via the middle cardiac vein in pigs

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Background: Conventional electrodes placed in middle cardiac vein (MCV) have previously been shown to reduce the defibrillation threshold (DFT) compared to standard electrode configurations in pigs. We have further evaluated DFT reduction in the same setting but using custom built bi-filament defibrillation electrodes {ELA Recherché, Paris, Fr} (placed in MCV) with novel design features intended to optimise energy delivery and defibrillation efficacy.
Methods and Results: In 9 pigs (61.3±4.3 kg) defibrillation electrodes were deployed under fluoroscopic control, into right and left branches of MCV. VF was induced (4sec bursts 50Hz AC). 2 animals could not be resuscitated from VF by external shocks after failed internal defibrillation and were excluded from analysis. In 1 MCV anatomy was unsuitable for electrode deployment (venous anatomy defined by contrast injection). A customised guide catheter selectively cannulated venous radicles for defibrillation electrode placement. The DFTs of the following configurations were evaluated using a binary search method:

DFT by configuration

Configuration	RV to Can	RV to SVC+Can	RV+MCV to Can
DFT (Joules)	22.8±7.3	21.9±7.6	13.1±5.1

$p<0.05$ RV to can vs RV + MCV to can

Conclusion: The addition of a bifilament electrode in separate branches of MCV reduces DFT by 43% compared to conventional configurations. Optimisation of electrode design may further reduce defibrillation requirements.

P3481 14–20% of patients with an implantable cardioverter-defibrillator indication may benefit from resynchronisation therapy

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Treatment of congestive heart failure (CHF) aims for symptomatic relief and reduction of mortality. An implantable cardioverter defibrillator (ICD) prevents sudden death in patients at high risk, whereas recent data suggest that biventricular (BV) pacing in patients with CHF may improve functional status. The combination of these 2 treatments may be synergistic. It is unknown however, what percentage of patients with an ICD indication are potential candidates for BV pacing.
Accordingly, we retrospectively analyzed all patients who received an ICD, for eligibility of BV pacing. Based on the available literature, established criteria for BV pacing included NYHA class III or IV (> 6 months), dilated cardiomyopathy of any origin and a QRS duration >120 ms. Patients in NYHA class II with a left ventricular ejection fraction (LVEF) <30% and QRS >120 ms were also considered eligible. The incidence of potential exclusion criteria, including atrial fibrillation (AF), RBBB and PR interval <150 ms, was also assessed.
Results: 195 consecutive patients received an ICD from June 1996 till July 1999 at our hospital. There were 159 men and 36 women, with a mean age of 59 ± 13 years. Underlying cardiac disease was ischemic (66%), idiopathic dilated cardiomyopathy (CM) (13%), primary CM (8%) and miscellaneous in 13% of the patients. Indications for ICD implantation were out hospital cardiac arrest (52%), ventricular tachyarrhythmia (46%) and preventive (2%). In the 195 patients the mean LVEF was 36 ± 17.
The incidence of severe CHF (NYHA class III/IV) was 19% (37 patients); 32 (16%) patients were in NYHA class II with an LVEF <30%. Of these 69 patients, 39 had a QRS duration >120 ms (18 LBBB, 9 RBBB, 12 intraventricular conduction delay). Thus, a total of 39 (20%) patients were eligible for BV pacing in addition to an ICD. When patients either in chronic AF or with RBBB were excluded, this number was reduced to 27 (14%). None of the patients had a PR interval <150 ms (mean 196 ± 31ms, range 160 - 260).
In conclusion, 14-20% of patients with an ICD indication may also benefit from BV pacing. Screening for eligibility of BV pacing should be considered in patients with CHF scheduled for ICD implantation.

ATRIAL FLUTTER – ABLATION

P3482 Catheter ablation of the right atrial cavo-tricuspid isthmus in patients with paroxysmal atrial fibrillation

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Patients with paroxysmal atrial fibrillation (pAF), who develop atrial flutter during treatment with class IC drugs, benefit from a cavo-tricuspid ablation of the isthmus. It is unknown whether patients with AF may also benefit from this procedure independently of the occurrence of drug related atrial flutter. Therefore we included in this study highly symptomatic patients with pAF. At least one month prior to the ablation patients underwent twice Holter-monitorings and event recordings. All patients were instructed to record their arrhythmia episodes. The documentation of atrial flutter led to the exclusion of the patients. After the ablation all recordings were repeated the subsequent 6 months. If the patient took any antiarrhythmic drug before the procedure, the drug was continued the whole follow-up period.
Results: 25 patients with pAF were included into the study (age: 55±9 years), 4 patients suffered from structural heart disease (EF 55 ± 8%). None of the patients had dilated atria in the echocardiography. In all patients the isthmus ablation was successfully performed. During the follow-up of 6±3 months 12/25 patients reported to feel an significant improvement of arrhythmia symptoms. They reported less frequent and less severe episodes of AF. Patients benefitted most from ablation if the episodes of AF prior to the intervention occurred with a heart rate > 100 b/min. ECG pattern such like polymorphic (flutter-like) p-waves during AF were not predictive for the patient outcome. Conclusion: Almost 50% of the patients with pAF benefit from a cavo-tricuspid isthmus ablation. Macroreentry circuits around the tricuspid annulus seem to play an important role in sustaining AF. Thus a minimal linear lesion within the cavo-tricuspid annulus might be an alternative less aggressive symptomatic approach in patients with pAF than multiple linear lesions or focal ablation procedures.

P3483 Impact of first-line radiofrequency ablation in patients with atrial flutter on the risk of subsequent atrial fibrillation

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Background: Radiofrequency ablation (RFA) of Atrial Flutter (AFlu) has been effective for short and intermediate term arrhythmia control. However, it is unknown if first-line RFA will alter the intermediate-term risk of developing atrial fibrillation (AFib). Objectives. The aim of this study was to evaluate the long term risk of subsequent AFib after RFA in two groups of pts with lone AFlu, Group I: first-line RFA therapy and Group II: RFA after at least one drug therapy failure. Lone AFlu excluded prior evidence of AFib. Methods. During 24 months, 161 consecutive patients (66±12 years; 29 females) with counterclockwise A Flu were considered eligible, 92 pts in GpI (68±12 years) and 69 pts in GpII (65±11 years). RF-ablation with an 8-mm-tip catheter was performed by the same operator and the end-point was to obtain a bi-directional block. Results: The mean follow-up for the entire population was 15±9 months and cumulative risk of AFib was analyzed by use of the Kaplan-Meier method and by the log-rank test. Clinical presentation, electrophysiologic data, results of RF ablation and follow-up were as following in the two groups (*p<. 05): flutter duration since-onset (1.9±3 vs 28±31 months; p<.0001), structural heart disease (40 vs 40.5%; ns), left ventricular ejection fraction (58±12 vs 61±10%; ns), left atrial size (43±7 vs 41±6mm; ns), cavo-tricuspid isthmus dimension (40±10 vs 37±11 mm; ns), bi-directional block (98.9 vs 94.2%; ns), RF application (12.4±.12 vs 12.1±12 minutes; ns), AFL recurrence (4.3 vs 7.2%; ns), discharge with antiarrhythmic agents (10/92 vs 14/69; p=.4), mean follow-up (14±8 vs 16±9 months; ns), atrial fibrillation occurrence (6.5% vs 11.5%; p=.4). No complication were noted in the two groups. Conclusions. This study suggests that first-line therapy of AFlu with RF ablation does not alter the intermediate-term risk of subsequent AFib.

P3484 Safety of the complete line between the tricuspid ring and the inferior vein cava during the ablation of the cavotricuspid isthmus

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Complete linear atrial ablation is necessary to achieve successful ablation of atrial flutter. Experimental studies have shown that deeper and wider lesions can be safely performed using 8 mm or irrigated-tip catheters. However, the lesions created by these catheters may be more than 10 mm in diameter and depth. The potential advantages of these catheters would include a quicker ablation, with a higher success rate. However, the potential damage to the tricuspid valve or inferior vena cava has not been evaluated.
Twenty-seven pigs (weighing between 26 and 52 Kg) were ablated. Standard RF ablation was performed with a steerable 4-mm tip, 7 Fr catheter, Marinr, (Medtronic Inc., Minneapolis, USA). The RF Generator was Atakr II, Medtronic. The application was carried out in a temperature-controlled mode, targeting 70°C. The Irrigated tip catheter was a Chilli (Cardiac Pathways). We used 50 watts, temperature-controlled mode, 50°C. The 8 mm Catheter was a Conductor from Medtronic, the power used was 100W. The three types of ablation were chosen randomly. After 1 week, the animals were slaughtered. A total of 187 radiofrequency applications were made in 26 animals, using the three different catheters (10 Irrigated, 8 standard, 8 catheters 8 mm).
The size of the lesion was greater with the irrigated tip catheters and the 8 mm than with standard. The line of anatomic isthmus block was documented. Completely transmural lines were found in 14 animals. The lesion appeared as a discoloured greyish red oval area, sharply demarcated from the adjacent healthy endocardium. In 7 animals (1 Irrigated, 4 with 8-mm catheters, 2 standard), the lesions extended to the right ventricle and the tricuspid valve. The tricuspide valve was severely damaged in 2 pigs and with mild lesions in 5. The animals with tricuspid lesions had a higher maximal power (59± 27 Watts versus 51 ± 24 watts) and temperature (63± 4°C versus 55± 11 °C), p < 0.001. The Low Energy Measurement (LEM), was also higher (0.55±0.24 versus 0.35±0.29, p 0.001), indicating a greater pressure contact of the catheter.
Conclusions: The tricuspid valve may be severely affected by the application of radiofrequency during the ablation of atrial flutter. This fact was particularly documented after using high energy (100 Watts) with 8-mm catheter (50% cases), but can be produced after using usual energy with standard catheter (20% cases). In order to avoid this damage, it is neccessary to avoid applications inside the right ventricle.

P3485 Anatomic evaluation of inferior vena cava-tricuspid isthmus: correlation between angiography and transthoracic echocardiograpy

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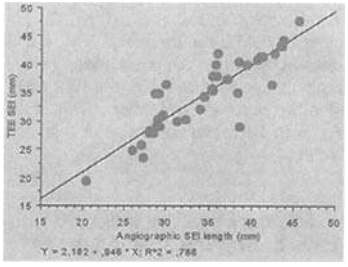
Background: In patients with common atrail flutter, bidirectional conduction block across the sub.eustachian isthmus (SEI) often requires excessive radiofrequency applications due to the length of this region. Gaining information about SEI length can guide the ablation approach (catheter choice). Anatomic evaluation is generally performed by right atrial angiography (RAA), however this technique is invasive, expensive, time consuming, and special equipment is required with contrast injection. We hypothesized that transthoracic echocardiography (TTE) may constitute an alternative to RAA. Objectives. The aim of this study was to assess the value of TTE in comparison with RAA, the gold standard. Methods. This study prospectively included 41 consecutive pts (65±13 years; 4 women) presenting a common atrial flutter and referred for ablation over 4 months period. The SEI length was measured as the distance from the lateral margin of the tricuspid annulus to the inferior vena cava origin in the subxiphoid view. RAA was performed in right anterior oblique view (25°) and the SEI was measured between the inferior vena cava and the lower hinge point of the tricuspid valve. Results. TTE was feasible in 39/41 pts (95.3%). SEI length correlation coeffitients between the two methods were 0.89 ($p<.0001$).



Correlation graph.

Conclusions: This study demonstrates that non invasive measurement of SEI length by TEE is feasible and highly correlated with the angiographic approach. TTE can be used to assess SEI length before ablation of atrial flutter gaining information about catheter ablation choice.

P3486 A non-fluoroscopic real-time 3D-navigation system allows easy and safe treatment of typical atrial flutter

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The ablation of the cavotricuspid isthmus using radiofrequency (RF) is a well established procedure for treatment of isthmus dependent typical atrial flutter. Nevertheless, fluoroscopy times are high and recurrence rate remains significant. The new non-fluoroscopic intracardiac navigation system (LocaLisa3, Medtronic) allows for the first time a real-time localization of up to 4 additional catheters without fluoroscopy. Furthermore this navigation system allows exact marking of the ablation position and online controlling of the catheter's position even during RF application. This enables the physician to induce an accurate and continous lesion.

Methods: Twenty-two consecutive patients with typical atrial flutter scheduled for isthmus blockade were included. 11 patients were treated conventionally (point-by-point lesions in the septal isthmus, Marinr-4mm,70°,70W), 11 patients were ablated with the same method combined with the LocaLisa (LL)-system.

Results: The fluoroscopy time of the LL-group (8.8±4.42) min was significantly reduced compared with the control group (18,3±12 min, $p<0.01$). The duration of the procedure was 120 ±38min in the control group versus 140 ±44min ($p>.05$) in the LL-group. The efficacy of the ablation to create a complete isthmus blockade was higher using the LL-system: In 9/11 patients of this group the isthmus blockade was complete after the first lesion while in all patients of the control group gap mapping guided additional RF applications were necessary. Moreover the complication rate was lowered in the LL-group: No complication was found in the LL-group, while a temporary AV-block III appeared in 1 patient of the control group.

Conclusions: The real time 3D-navigation system LocaLisa 3 improves the safety of isthmus blockade for typical atrial flutter. The system provides easy documentation of the RF-lesions and re-navigation to former localized gaps without additional fluoroscopy. Therefore, it reduces significantly the fluoroscopy time with insignificant increase of procedure times.

P3487 Outcome of atrial flutter ablation: results from the venetian multicenter study

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Radiofrequency transcatheter ablation is a well-established procedure for atrial flutter treatment. However early and late outcome of this technique has not been fully investigated in large cohort of patients.

Methods: Radiofrequency ablation of atrial flutter was performed in 417 consecutive patients (103 female, 314 male; mean age 62 years, range 21-86) in six cardiology centers of Northeast of Italy from 1997 to 2001. Eight-mm tip catheter was employed in 337 cases, irrigated tip in 28 cases, 4mm tip in 27 cases, and 4+4mm tip in 25 cases. Inferior isthmus ablation (between tricuspid anulus and inferior vena cava) was performed in 322 patients (77%), while septal isthmus (between tricuspid anulus and coronary sinus ostium) or both isthmus ablation was performed in 95 patients (23%). Successful procedure was considered when bi-directional isthmus block was achieved.

Results: Success was achieved in 367 cases (88%). Success rate was lower using 4 mm catheter tip (52% vs 84% [4+4mm], 89% [irrigated], 91% [8mm]; $p<0.001$) and in earlier years (70% [1997], 87% [1998], 87% [1999], 90% [2000], 95% [2001]; $p<0.01$). Complications occurred in 7 patients (1.6%): 1 patient had polymorphic ventricular tachycardia during the procedure, 4 patients developed vascular complication in early post-interventional period, 2 patients (0.5%) developed complete AV block during the procedure requiring pace maker implantation. Both patients with AV block underwent septal isthmus ablation (2.1%), while no AV block occurred in patients who only underwent inferior isthmus ablation ($p<0.05$). During a mean follow up of 19 ± 36 months, atrial flutter recurred in 41 patients (9.8%). Recurrence rate was significantly higher in patients who underwent ablation with 4 mm tip comparing with 8 mm, irrigated or 4+4 mm tip catheter (11/27, 41% vs 27/337, 8%, 2/28, 7% and 1/25, 4% respectively; $p<0.001$).

Conclusions: Our data confirm that transcatheter radiofrequency ablation is a safe and effective technique for atrial flutter treatment. Four mm catheter tip should be avoided in order to increase the success and to reduce the recurrence rate. Moreover septal isthmus ablation should be avoided due to a small but significantly higher risk of complete AV block.

P3488 Ablation of typical atrial flutter using ultra sound 3D RPM mapping – long-term results

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RPM is a non-fluoroscopic electro-anatomical mapping system for ablation of typical atrial flutter. In this series of 15 patients (CL 221.7 ± 20.8 ms, EF 58.2 ± 7.9%, LA 43.5 ± 4.4 mm), the ultrasound multi-transducer catheters of the RPM Mapping System (Cardiac Pathways, Realtime Position Management ™ System) were securely placed in the coronary sinus and at the right ventricular apex. The movement of the cooled steerable ablation catheter (Cardiac Pathways, Chilli rpm ™) which is also equipped with ultrasound transducers, could be depicted on the monitor at any time. Several guiding marks were set in the right atria and thus, defined the subsequent lesion lines (i.e. sinus coronarius, V. cava inferior, septal tricuspid annulus). In all 15 patients bi-directional block was achieved after 10.2 ± 6.3 single applications. The total time of intervention amounted to 102 ± 31 min. There was a strong learning curve with regard to the reduction of x-ray exposure time (last 5 patients 4.9 + 2.1). No complications occurred. The mean follow-up period was 13.9 ± 5.5 months. Rhythm follow-up data show 90% sinus rhythm, 10% atrial fibrillation, and no new recurrence of typical atrial flutter.1 patient died (non-cardiac death).

Isthmus ablation with ultrasound navigated catheters is feasible and safe. After a learning phase, the precision of linear lesions was improved and fluoroscopic exposure time considerably reduced.

P3489 Catheter-based cryoablation of atrial flutter: chronic success rate comparable to RF ablation and a painless procedure

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Background: Radiofrequency (RF) ablation of type I atrial flutter (AFL) has a high procedural success rate (96%) and low recurrence rate (6-9%). However, RF ablation of the right atrial isthmus (RAI) can be painful. The aim of this study was to assess the acute and chronic efficacy and procedural pain for cryoablation (cryo) of AFL.
Methods: Thirteen pts (52 ± 11 years, 11 men) with AFL (AFL only = 4; atrial fibrillation organized into AFL under antiarrhythmic drugs: class IC = 7, amiodarone = 2) underwent cryo of RAI using point-by-point applications. Mean left atrial size and LVEF was 45 ± 6 mm and 58 ± 10%. Cryo was performed with the CryoCor cryoablation system using a pre-cooler and N2O as refrigerant. Cryothermia was delivered twice, for 4 minutes, at each site along the RAI. Pain was evaluated after every application using a visual analogue scale ranging from 0 to 100.
Results: All pts were successfully ablated at a median of 8 sites (median 16 applications) along the RAI with nadir temperatures between -71 and -90°C (mean -83.4 ± 5.7°C). The fluoroscopic and procedural time was 35 ± 14 min and 3.9 ± 1.1 h. Pts did not perceive pain during the freezes. After a mean follow-up of 5 ± 3 months no recurrences of AFL occurred.
Conclusions: The acute and chronic success rate obtained with cryo of the RAI for AFL is at least as high as that seen with RF ablation. Furthermore, cryo of RAI is painless.

P3490 Irrigated-Tip versus 8-mm-Tip catheters for ablation of atrial flutter in patients with cavo-tricuspid isthmus > 35 mm. A randomized study

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Background: Radiofrequency ablation (RFA) lesions are expected to be deeper with a Cooled RFA catheter (cRFA) and longer with a conventional 8mm tip catheter in patients with common atrial flutter (AFlu). It has been demonstrated that cavo-tricuspid isthmus (CTI) length may influence RFA duration. Randomized studies comparing these two RFA catheters are lacking, especially when CTI is broad. Objective. The purpose of this prospective study was to compare the efficacy and safety of these catheters for AFlu ablation in a sub-group of patients with Cavo-Tricuspid Isthmus > 35 mm. Methods. Forty-nine consecutive patients were screened and a right atrial (RA) angiography was performed before RFA. Population was divided in two groups, pts with CTI > 35 mm (n=23) and pts with CTI < 35 mm (n=24). Informed consent was not obtained from 2 pts. Patients with CTI > 35 mm were randomized to ablation with 8-mm thermocouple catheter (Saint-Jude medical) (Gp I; n=12) or irrigated 5-mm-tip thermocouple catheter (Cordis Webster Thermocool) (Gp II; n=11). RFA using an 8 mm tip ablation catheter (Boston Scientific) was performed in pts with CTI < 35 mm. The same operator performed all procedures. A 12-pole catheter was positioned in the lateral RA (LRA: pole 11-12) along the isthmus (pole 7-8; 5-6; 3-4) with its distal electrode pair in the coronary sinus origin (CSO; pole 1-2) to assess during pacing (600 ms cycle length) from pole 11-12 and pole 1-2 the complete bi-directional block. When the complete bi-directional block was not obtained after 30 minutes of RF application, a crossover was required. Results: Clinical presentation and results of RF ablation were as following between GpI (70±6 years) and GpII (70±10 years): history of AFib before ablation (4/12 vs 4/11; ns), structural heart disease (5/12 vs 7/11; ns), LV EF (59±11 vs 56±14%; ns), left atrial size (47±7 vs 49±9 mm), cavo-tricuspid isthmus dimension (39±3 vs 40±3 mm; ns), bi-directional block (96.2 vs 100%; ns), RF application (18±19 vs 20±16 minutes; ns), fluoroscopic time (19.8±16 vs 19.8±19 minutes; ns), recurrence of bi-directional block within 30 min (1/12 vs 4/11; ns), RF failure (0/12 vs 1/11; ns), crossover (3/12 vs 2/11; ns). No complication occurred. Conclusions. Preliminary results of this prospective pilot study demonstrate a similar success between cRFA and 8 mm tip catheter when Cavo-Tricuspid Isthmus is >35 mm.

P3491 Incidence, mechanisms and treatment strategies of atrial flutter following intraoperative radiofrequency ablation of atrial fibrillation (IRAAF)

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Intraoperative radiofrequency ablation has evolved a highly effective curative therapy for atrial fibrillation (AF). The IRAAF treatment concept (induction of contiguous left atrial lesion lines between the mitral annulus and the ostia of the pulmonary veins) was applied in 387 patients (pts.), in 129 pts. with AF as primary indication (group I), in 117 pts. in conjunction with minimal invasive mitral valve repair or replacement (group II), in 46 pts. with mitral valve surgery via stemotomy (group III) and in 95 pts. with other cardiac surgeries (group IV). In all pts. of group I and II the procedure was performed via minimal invasive surgical techniques (right lateral mini-thoracotomy). Freedom of AF at 6 months follow-up was 97% in group I and 87% in group II. However, 5% of pts. of group I and 7% of pts. of group II developed recurrent episodes of atrial flutter during longterm follow-up. Invasive electrophysiologic study with non-fluoroscopic mapping technology (Carto, Biosense Webster) was performed in 12 pts.. Cycle length of atrial flutter was 271±48 ms. In 3 pts. the arrhythmia mechanism was isthmus related typical atrial flutter although the surface-ECG indicated atypical flutter. These pts. underwent successful isthmus ablation. In 6 pts. left atrial re-entry evident from detailed entrainment mapping was the arrhythmia mechanism. Using 3D-electromagnetic mapping the complete left atrial re-entrant circuit could be mapped and reconstructed. Gaps in the IRAAF-lesion lines giving rise to left atrial re-entry were identified and radiofrequency application to the gap sites terminated the tachycardias in 5 of 6 cases. One pt. presented with left atrial re-entry and with typical atrial flutter, both treated successful with ablation. In 2 pts. ectopic atrial tachycardias (EAT) were revealed. In the one case the EAT originated in the AV-nodal area and in the other case in the region of the crista terminalis. Both EATs were successfully ablated. Conclusions: Atrial flutter following intraoperative ablation of AF occurs in approximately 10% of pts. treated. In the majority the flutter is due to gaps in the induced lesion lines. These gaps can be identified using 3D-electromagnetic mapping and radiofrequency ablation of gap sites cures pts. from atypical flutter. However, even if the surface-ECG suggests atypical flutter, isthmus related flutter may be present. The atypical appearance of the flutter waves in the surface-ECG in these pts. may be explained by an unusual left atrial activation due to the intraoperatively induced lesion lines.

CONTROL MECHANISMS IN MYOCARDIAL HYPERTROPHY

P3492 Unchanged expression of marker proteins of the calcineurin pathway in rats overexpressing the mouse renin gene (TG (mREN-2)27)

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Cardiac hypertrophy is an adaptive response to many cardiac diseases with an increased afterload. While the hypertrophic response is initially a compensatory mechanism, sustained hypertrophy can lead to dilated cardiomyopathy and heart failure.
It has been argued, that various stimuli (e.g. endothelin, RAAS) finally lead to cardiac hypertrophy via a calcineurin dependent pathway. It has also been shown that in transgenic mice expressing activated forms of calcineurin or transcription factor NF-AT3 an inhibition of the calcineurin phosphatase activity with cyclosporin A (CyA) stopped the development of cardiac hypertrophy. Nevertheless, other studies failed to show an influence of CyA on the development of cardiac hypertrophy (e.g. in rats wit aortic banding).
To further elucidate the role of the calcineurin pathway in the development of cardiac hypertrophy we measured the expression of marker proteins of the calcineurin pathway (calcineurin, NF-AT3, GATA4) and the calcineurin activity in transgenic rats (TGR, n=10) with hypertension induced myocardial hypertrophy because of an overexpression of the mouse renin gene (TG(mREN-2)27). As control group we used age matched Sprague-Dawley rats (n=10).
Western blotting showed no significant diference in protein expression of calcineurin (TGR 86 ±9,9 DU, control 91 ±2,4 DU=Densitometric Units), GATA4 (TGR 13,6 ±0,9 DU, control 9,9 ±1,8DU) or NF-AT3 (TGR 100,5 ±1,0 DU, control 98,1 ±1,5 DU). The rt-PCR confirmed the equivalent results between TGR and control group on mRNA level. In addition we measured the calcineurin activity with a phosphatase assay and found no difference between TGR and control, too. In conclusion, we could not find an activated calcineurin pathway in transgenic compared to Sprague-Dawley rats.
Thus, at least in this renin overexpressing rat model, cardiac hypertrophy may result from a calcineurin independent stimulation.

P3493 Differential regulation of the calcineurin genes in human cardiac hypertrophy and in ischaemic and dilated cardiomyopathy

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In some animal models of cardiac hypertrophy and heart failure, the dimeric phosphatase calcineurin (Cn) is upregulated in the myocardium. Its targeted inhibition prevented myocardial hypertrophy and failure. The isoforms of the catalytic subunit CnAalpha, beta and gamma and CnB are differentially regulated by hypertrophic stimuli. In order to characterize different forms of human myocardial hypertrophy, we determined the CnAalpha, CnAbeta(β) and CnB mRNA together with markers of hypertrophy (ANP, BNP) in samples from patients with cardiac hypertrophy due to aortic stenosis and with heart failure due to dilated (DCM) and ischemic cardiomyopathy (ICM).

We measured CnAalpha, CnAβ, CnB, ANP and BNP mRNA in left ventricular samples taken during aortic valve surgery from 10 patients with aortic valve stenosis (AS, n=10, LV EF: 44 ± 6%) and from explanted failing hearts from patients with DCM (n=27) and ICM (n=7) after informed consent. As controls, 15 unused donor hearts with normal systolic function were used. mRNA was quantitated by real-time PCR (PE 5700). Target gene mRNA was related to the stably expressed GAPDH mRNA from the same sample. Data are given as medians; Kruksal Wallis and Wilcoxon tests were used.

Differential upregulation of the isoforms of the catalytic subunit CnA was found. CnAalpha was sign. increased in AS (194% of con, $p<0.05$), but not in DCM (120%) and not in ICM (102%). CnAβ mRNA was increased in AS (215%) and DCM (188%, $p<0.0.01$ both), but not in ICM (126%). The regulatory subunit CnB exhibited a tendency towards a decrease in AS (50% of con, ns) and ICM (79%, ns) with a great interindividual variability. In contrast, CnB was significantly upregulated in DCM (292%). ANP and BNP mRNA were upregulated in AS and DCM, but correlated only weakly with the Cn genes.

The regulation of CnA and CnB genes and their subunits is different in human cardiac hypertrophy, ICM and DCM and may represent a useful marker for the transition from compensated hypertrophy to heart failure or even a clue for their differentiation at a molecular level.

P3494 Pressure-overload cardiac hypertrophy in mice with a gene-targeted disruption of the NADPH oxidase subunit gp91phox

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Increased oxidative stress is suggested to be involved in the pathophysiology of left ventricular hypertrophy (LVH). We have previously shown that a phagocyte-type NADPH oxidase that generates reactive oxygen species (ROS) is expressed in the heart and plays a pivotal role in the cardiac hypertrophic response to angiotensin II. In this study, we investigated the response to pressure overload in gene-modified mice lacking the gp91phox subunit of NADPH oxidase (which is critical for ROS generation) and matched wild-type controls (C57/BL6J).

Adult male wild-type and gp91phox knockout mice (16-20g) underwent suprarenal abdominal aortic banding (8.0 nylon suture tied around a 29 gauge needle; ~70% constriction) or sham surgery. One week post-surgery, the LV/body weight ratio was ~25% higher in wild-type bands versus shams (3.91 ± 0.13 vs 3.14 ± 0.11; $P<0.05$) and ~27% higher in banded gp91phox-/- mice versus shams (4.29 ± 0.05 vs 3.38 ± 0.11; $P<0.05$; n=4 per group). At 2 weeks post-op, LV/body weight ratio was 42.5% higher in banded wild-types (4.57 ± 0.29 vs 3.21 ± 0.07) and 43.2% higher in banded knockouts (4.87 ± 0.18 vs 3.4 ± 0.07) versus respective sham controls. Expression of atrial natriuretic factor mRNA (semi-quantitative RT-PCR) was higher ($P<0.05$) in both banded groups relative to their sham controls (wild-type: 16.7 ± 2.1 vs 2.3 ± 0.1 densitometric units; gp91phox knockouts: 19.3 ± 3.6 vs 2.9 ± 1.5 units). NADPH-dependent O2- production was measured in LV homogenates by lucigenin (5μM)-enhanced chemiluminescence. Wild-type banded mice had higher O2- production cf. the sham group (3.85±0.24 vs 2.77±0.31 arbitrary light units; P=0.07, n=6). The banded gp91phox-/- animals also had a similar increase in O2- production compared to their sham controls (5.82 ± 0.55 vs 2.88 ± 0.52 arbitrary light units; $P<0.05$). NADPH-dependent O2- production was inhibited by the flavoprotein inhibitor diphenyleneiodonium in all groups but not by L-NAME.

Conclusion A similar increase in LV mass is seen in both wild-type and gp91phox-deficient mice in response to pressure overload. The increase in LV NADPH oxidase activity in banded gp91phox-/- mice suggests that a non-gp91phox-containing oxidase contributes to ROS production during pressure overload. Whether this ROS production is involved in the development of LVH merits further study.

P3495 Heart rate variability in two different patterns of left ventricular hypertrophy and geometry

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In this study, we investigated the heart rate variability (HRV) indexes in two different types of left ventricular hypertrophy (LVH) model as in patients with hypertrophic cardiomyopathy (HCM) and essential hypertension. There were 25 patients (m/f: 11/14, mean age: 48±9) in HCM group, 25 patients (m/f: 10/15, mean age: 51±7) in hypertensive left ventricular hypertrophy (HLVH) group and 25 healthy subjects (m/f: 12/13, mean age: 50±4) in control group. After the echocardiographic examination, all patients underwent 24 hours Holter ECG monitoring for the assessment of HRV indexes (pNN50, RMSSD and SDNN). The SDNN, RMSSD, pNN50 values from the HRV indexes are compared for the three groups (HCM, HLVH and control groups), differences between groups are found reasonable. SDNN (msec), RMSSD (msec), pNN50 (%) values (130.56±17.6, 28.4±10.4 and 6.5±4.0 respectively) in HCM group were found significantly lower than the control group (156.1±27.7, 44.1±19.8 and 12.8±8.1 respectively, $p<0.05$). There was no significant difference between HLVH and control groups for the SDNN index of HRV (137.8±33.6 versus 156.1±27.7 msec). However RMSSD and pNN50 indexes reflecting parasympathetic tonus were found as reasonably lower in HLVH group than control group (30.8±13.0 versus 44.1±19.8 msec and 8.1±6.3 versus 12.8±8.1%, respectively, $p<0.05$). No significant difference for the HRV indexes was detected between the HCM and HLVH groups. We couldn't find any relationship between HRV indexes and left ventricular outflow track obstruction, arrhythmias and syncope in HCM and HLVH patients. There was negative correlation between parasympathetic parameters of HRV and left atrial dimensions in HCM group, but not for HLVH group.

	HCM	HLVH	CONTROL	P
Heart Rate(msec)	76±9	73±14	75±8	n.s.
Mean RR(msec)	761.3±70.2	780.5±90.8	795.1±79.1	n.s.
SDNN(msec)	130.5±17.6	137.8±33.6	156.1±27.2	0.004
RMSSD(msec)	28.4±10.4	30.8±13.0	44.1±19.8	<0.001
PNN50(%)	6.5±4.0	8.1±6.3	12.8±8.1	0.002

In conclusion; HRV indexes are decreased in patients with left ventricular hypertrophy. The shape of hypertrophy doesn't seem to have an effect on HRV indexes. HRV parameters could not be used as predictors of the arrhythmias and syncope in patients with HCM or HLVH.

P3496 Different actions of irbesartan and atenolol on cardiac repolarisation in hypertensive left ventricular hypertrophy

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Purpose: Left ventricular hypertrophy (LVH) is associated with a substantial risk for malignant arrhythmias and sudden death. The effects of antihypertensive therapy on QT dispersion, which reflects cardiac repolarization heterogeneity, in relation to changes in left ventricular mass are not well studied.

Subjects and Methods: Ninty two hypertensive patients with LVH were randomized double-blind to receive the angiotensin II type 1 receptor blocker irbesartan (n=44) or the beta1-receptor blocker atenolol (n=48) for 48 weeks. An age and gender matched control group consisted of 37 hypertensive subjects without LVH. Echocardiography and electrocardiogram(standard 12 lead, 50 mm/s)were performed at 0, 12 and 48 weeks. QT intervals were measured with a digitizing table by one person in a blinded fashion.

Results: Left ventricular mass index related to QT dispersion ($r=0.34$, $p<0.001$) and the duration of ventricular repolarization (the JT interval) but not the depolarization (the QRS interval) was dependent on the degree of LVH. The reduction in left ventricular mass was greater by irbesartan than by atenolol (-27±28 vs. -15±21 g/m^2 at 48 weeks, $p=0.021$), by similar reductions in blood pressure. Irbesartan decreased QT dispersion (from 56±24 to 45±20 ms at 48 weeks; $p<0.001$), and QTc dispersion (from 57±24 to 44±19 ms at 48 weeks; $p<0.001$). In contrast, atenolol had minor effects. Thus, decreases in QT and QTc dispersions were greater by irbesartan than by atenolol ($p=0.001$ and $p=0.011$, respectively), also when changes in left ventricular mass, blood pressure and heart rate were included in multivariate analyses.

Conclusion: Heterogeneity of ventricular repolarization is related to the degree of myocardial hypertrophy. Irbesartan, but not atenolol, reduces QT and QTc dispersions independent of changes in left ventricular mass, blood pressure, or heart rate. Thus, irbesartan may induce structural and electrical remodeling in a direction that could decrease the risk of fatal events in hypertensive patients.

P3497 Angiotensin II increases cell-matrix-interaction by activation of integrin-associated kinases in cardiac fibroblasts

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Activation of the cardiac renin angiotensin system is leads to proliferation of cardiac fibroblasts and myocardial fibrosis. Angiotenin II (AngII) induces synthesis of matrix- and adhesion proteins by cardiac fibroblasts. We have demonstrated that receptors for matrix proteins, integrins, are induced in a model of cardiac hypertrophy. In the present study we investigated the effect of AngII on β1-integrin mediated adhesion and cell contractility on collagen I (Col1), collagen III (Col3) and fibronektin (Fn) in cardiac fibroblasts from adult rat hearts (CFBs). Adhesion and cell contractility (measured by a spreading assay) is mainly mediated via auf β1-Integrin on these meatrices. A blocking antibody against β1-Integrin (50μg/mL) inhibited adhesion by 55% (Col3) and 85% (Col1, Fn). Spreading was blocked to comparable amount by this antibody. Treatment of CFBs with 1 μM AngII for 2 to 48 hours induced a concentration-dependent increase of adhesion to Col1 (2.2-fold, $p<0.01$), Col3 (1.9-fold, $p<0.01$) and Fn (2.4-fold, $p<0.01$). These effects have been blocked by the selective AT1 receptor-blocker irbesartan, but not by the AT2 receptor-blocker PD 123319. The effect of AngII was prevented by MAP Kinase inhibitor PD98059 and the PI3kinase inhibitor Wortmanin, which inhibits the activation of AKT. The effects of AngII were associated with the activation of integrin-assocoaited kinases. AngII induced the phosphorylierung of FAK (2-fold, $p<0.05$), Pyk2 (4-fold, $p<0.01$), AKT (3-fold, $p<0.05$) and MAP Kinase (5-fold, $p<0.01$) in CFBs. However, there was no significant change of β1-integrin mRNA in CFBs, nor an increased expression of β1, alpha1, alpha2 and alpha5-integrins after stimulation with AngII detected by flow cytometry. These data indicate, that the effect of AngII on adhesion is mediated via MAP Kinase and AKT, and leads to an increase of β1-integrin binding activity (avidity) whithout effect the xpression levels of integrin receptor in cardiac fibroblasts.

P3498 Changes in anisotropy associated with cellular architecture, and connexin43 expression in a guinea-pig model of left ventricular hypertrophy

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We have previously reported changes in conduction velocity and a reduction in anisotropy in left ventricular hypertrophy (LVH), and hypothesised that this results from changes in the topology of gap junctional coupling and cellular architecture as the principal determinants of intercellular conduction. LVH was induced in guinea pigs by a constrictive clip on the thoracic aorta. Papillary muscles were excised from banded and sham-operated animals 50 to 250 days post-operation. Conduction velocity (CV) was measured (by multiple intracellular impalements) in the longitudinal and transverse axes. Quantitative confocal immunodetection of Cx43 in 6 randomly selected highly confocal (<1mm) slices was performed. Cellular architecture was studied using serial sections. In LVH, there was an increase in cell size (LVH 407.5±106.4mm^2 and sham 278.3±76.2mm^2 $p=0.0027$), cell-to-cell contacts from 5.67±0.97 to 8.11±1.28 ($p<0.0001$) and in the number of intercalated disks per cell (8.22±2.16 to 10.22±1.22 $p<0.002$). However, the number of contacts between any two individual cells decreased from 1.46±0.34 to 1.24±0.15($p<0.02$). There was no change in the proportion of end-to-end connections or the number of intercalated disks per cm in both axes. In LVH Cx43 expression per cell correlated ($p<0.0001$ $r=0.76$ $n=20$) with an increased transverse conduction velocity (29.3 ± 9.6 cm/s vs. 20.5± 4.5 $p=0.007$) and with a corresponding decrease in transverse resistivity ($p<0.003$ $r=0.47$ $n=22$). However, there was no association between Cx43 expression per cell and either the reduced longitudinal conduction velocity (72.8±15.5 to 63.6±11.1 $p<0.05$) or the increased longitudinal intracellular resistivity (776±279 vs 411±124 $p<0.05$).

In LVH, an increase in transverse conductance resulting from an increase in cell to cell contacts, intercalated disks, cell size and Cx43 expression is associated with a corresponding increase in transverse conduction velocity and reduced anisotropy.

P3499 Electrophysiological remodelling in the diabetic heart: prevention by angiotensin II receptor blockade

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Electrophysiological abnormalities of the myocardium have been identified in diabetes, likely related with an increased risk of arrhythmias and sudden death. An upregulation of local renin angiotensin system occurs in human and rat diabetic heart. Since chronic stimulation of angiotensin II receptors (AT1) leads to cardiac remodeling in several physiopathological settings, we investigated the possible beneficial effect of AT1 blockade in a rat model of diabetes-related cardiomyopathy.

Methods: We analyzed the electrophysiological properties of ventricular cardiomyocytes (VCM) from diabetic rat hearts, with or without treatment with 20 mg/Kg/day losartan (LOS). Diabetes was induced by a single injection of streptozotocin (STZ, 55 mg/kg). One group of rats received LOS (STZ+LOS) in the drinking water beginning from 1 week before diabetes induction up to 3 weeks later. Age-matched rats, treated (Ctr+LOS) and not treated with LOS (Ctr), were used as controls. LOS treatment did not affect body weight, plasma glucose levels and water consumption of diabetic and control animals. Patch-clamped VCM were superfused with a normal Tyrode's solution (to measure action potential, AP) or appropriately modified Tyrode's solutions (to measure transient outward current, TO).

Results: Membrane capacitance, an index of cell size, was similar in all groups. Action potential duration at 90% repolarization (APD90) was significantly prolonged in STZ compared to Ctr rats (144±13 ms, n=28, vs. 106±10 ms, n=28, $p<0.05$). All the other AP parameters were unchanged. APD prolongation was paralleled by a significant decrease of maximum TO density in the STZ group (Ctr: 19.3±2.4 pA/pF, n=23; STZ: 12.6±1.4, n=34 pA/pF) ($p<0.05$). Pretreatment with LOS did not affect AP profile in Ctr rats, but significantly shortened its duration in diabetic rats: APD90 was 100±11 ms in STZ+ LOS rats (n=20; $p<0.05$ vs. STZ). The effect was comparable also at higher driving rate (1 Hz instead of 0.2 Hz), APD90 being 153% of Ctr in STZ cells and 113% of Ctr in STZ+LOS cells ($p<0.05$ vs. STZ). Normalization of APD by LOS was accompanied by restoration of TO density, which recovered to 18.7±1.8 pA/pF in STZ+LOS (n=36, $p<0.05$ vs. STZ). Time constant of TO recovery from inactivation was similar in Ctr (33.1 ms), STZ (36.2 ms) and STZ+LOS rats (35.9 ms).

Conclusions: these results demonstrate that AT1 blockade protects the heart from the development of electrophysiological alterations typically associated with diabetes, and suggest that it may represent a new therapeutic strategy against the arrhythmogenic risk in this setting.

P3500 Increased production of reactive oxygen species in hypertrophied myocardium: in vivo study by microdialysis technique

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There has been considerable interest in the role of reactive oxygen species in the pathogenesis of myocardial injury. The aim of our study was to investigate the production of oxygen free radicals in the myocardium of Wistar and Wistar-Kyoto rats and SHR-SP using microdialysis technique.

Methods: Experiments were carried out on anaesthetized open-chest male rats ventilated with oxygen from room air supplement. The linear microdialysis probe was inserted in the left ventricle wall and then perfused at the rate of 3 il/min with Ringer solution containing sodium salicylate. 2,3-dihydroxybenzoic acid (2,3-DHBA) produced in the reaction of oxygen radicals with salicylate was measured in dialysis samples by high-performance liquid chromatography and used as an indicator of the rate of oxygen radical production in myocardium.

Results: Dialysate sampling started 60 min after the probe implantation, and the baseline level of 2,3-DHBA was established in each experiment. Some quantity of 2,3-DHBA was always present in the perfusion fluid due to the exogenous salicylic acid oxidation. Mean baseline values of 2,3-DHBA in dialysate samples were not notably different (112±8.7%, n = 5) from the values of 2,3-DHBA in perfusion fluid in Wistar-Kyoto rats, but were significantly lower (87±3.2%, n = 6, $p < 0.03$) in Wistar rats and significantly higher (154±1.1%, n = 7, $p < 0.001$) in SHR-SP. We believe that this is the first report of in vivo registration of the elevated basal level of reactive oxygen species in hypertrophied myocardium of SHR-SP by high-sensitive microdialysis technique. The basal 2,3-DHBA in SHR-SP was positively correlated ($r = 0.83$, $n = 7$, $p < 0.05$) with degree of left ventricle hypertrophy expressed as a ratio of left ventricle weight to the body weight.

Conclusion: The results of our experiments demonstrate that the left ventricle hypertrophy in SHR-SP is accompanied by considerably higher rate of oxygen radical production.

GENE POLYMORPHISM IN CORONARY ARTERY DISEASE

P3501 PLA gene polymorphism in patients with acute coronary syndromes

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Platelet glycoprotein IIb/IIIa receptor plays an important role in platelet aggregation. Glycoprotein IIIa is polymorphic (PLA1 and PLA2), and the PLA2 variant may be strongly associated with increased risk of acute coronary syndromes. The protective role of acetylsalicylic acid (ASA) in ischemic heart disease is well known. ASA resistance can be detected in about 30% of the population, thus we routinely measure platelet aggregation in patients with acute coronary syndromes. The aim of our study was to examine the prevalence of PLA2 allele in acute coronary syndrome patients with or without ASA or ticlopidine resistance and in the healthy population. Methods: Prevalence of PLA2 gene was examined in 103 consecutive patients (31 females, 72 males, age: 61.1 ± 13.0 years) with acute coronary syndromes and in the healthy population using polymerase chain reaction (PCR). 30 of the 103 patients (29.1%) were found ASA or ticlopidine resistant (14 females, 16 males, age: 66.1 ± 8.5 years). Results: PLA2 polymorphism was found in 39.8% of patients with acute coronary syndromes, in 50.0% of acute coronary syndrome patients with ASA or ticlopidine resistance and in 15.6% of the healthy population. The prevalence in both patient groups was significantly higher than the prevalence in the healthy population ($p<0.05$). Among patients with acute coronary syndromes those having ASA or ticlopidine resistance have a significantly higher prevalence of PLA2 allele than non-resistant patients ($p<0.05$). Conclusion: Our results support the hypothesis that the PLA2 allele occurs more frequently in patients with acute coronary syndromes especially in those with ASA or ticlopidine resistance.

P3502 Gender-specific gene environment interaction between CA repeat polymorphism of eNOS gene and homocysteine in acute coronary syndromes

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The CA repeat polymorphism in intron 13 of the endothelial nitric oxide (eNOS) is associated with an excess risk of coronary artery disease. We have recently shown in 1000 consecutive patients with angiographically confirmed coronary artery disease and 1000 age- and gender-matched control patients that the presence of one allele containing >=34 CA repeats is associated with an excess risk of coronary artery disease.

Hyperhomocysteinemia (Hhcy) interacts by several mechanisms with the NO system favouring endothelial dysfunction and vasospasm. Since Hhcy appears to be an independent cardiovascular risk factor for acute coronary events, we investigated a possible interaction between Hhcy and the eNOS CA repeat polymorphism.

The median value of homocysteine (Hcy) in our study population was 9.4 μmol/l. Accordingly we determined the relative risk of acute coronary events for Hcy values > 9.4 μmol/l and < 9.4 μmol/l at different CA repeat cut off values (>=35, >=36, >=37, >=38, >=39 CA repeats). For the entire CAD group (n=1000) acute coronary syndromes (ACS) were not significantly associated with the CA repeat number. However, in females with Hcy >9.4 μmol/l the relative risk for developing ACS increased significantly from 1.7 (confidence interval 0.7-4.3; not significant) at cutoff >= 35 Ca repeats, 4.9 (1.7-13.6; p=0.003) >=36 Ca repeats, 11.2 (2.9-41.9; p<0.001) at >=37 CA repeats, to 18.3 (1.9-173.2; p<0.006) at >=38 Ca repeats. This effect modification was not observed in men.

These data suggest a gender-specific gene environment interaction between the CA repeat eNOS polymorphism and homocysteine in ACS.

P3503 Acute-phase levels of plasminogen activator inhibitor-1 (PAI-1) and the 4G/5G PAI-1 promoter polymorphism

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Background: The 4G/5G plasminogen activator inhibitor-1 (PAI-1) promoter polymorphism is known to modulate basal PAI-1 levels and to affect prognosis in severely traumatized patients. We hypothesized that the 4G/5G genotype might also influence the acute-phase levels of PAI-1 in patients undergoing coronary-artery surgery. As a secondary point, we assessed the association of PAI-1 genotype and PAI-1 levels with in-hospital course.

Methods: 111 stable patients with multivessel coronary artery disease undergoing elective coronary-artery by-pass grafting were investigated. Plasma PAI-1 activity and antigen levels were measured by ELISAs in samples taken before surgery, daily up to 72h, and at discharge. Serial levels of white-cell count, fibrinogen, C-reactive protein and interleukin-6 were also assessed. Plasma was collected in citrate with antiplatelet agents. Genomic DNA was extracted by standard procedures. The PAI-1 -675 4G/5G polymorphism was determined as previously described. Age >80 years, left ventricular ejection fraction <30%, urgent revascularization, renal, hepatic or respiratory insufficiency, active infection, and chronic anti-inflammatory therapy were reasons for exclusion.

Results: PAI-1 activity and antigen concentrations increased approximately two-fold after surgery, peaking at 48 hours. Carriers of the 4G-allele, compared with 5G/5G homozygotes, showed higher PAI-1 activity and antigen levels both preoperatively (P=0.007 and P=0.035) and after surgery. In multivariate analysis, 4G/5G genotype was the only significant modulator of postoperative PAI-1 activity (P=0.003) and the main significant modulator of postoperative PAI-1 antigen (P=0.013). The effect of genotype on PAI-1 was not specific for the acute-phase, as the interaction between time and genotype effects was not significant (i.e., higher postoperative levels reflected higher baseline values). PAI-1 concentrations (peak - baseline), but not PAI-1 genotype, correlated with length of stay in the intensive-care unit and in-hospital (P=0.0026 and P=0.0014 for PAI-1 activity, P<0.00014 and P<0.0001 for PAI-1 antigen), independently of age and of changes in white-blood cell count, fibrinogen, C-reactive protein and interleukin-6.

Conclusions: These data, in patients undergoing elective coronary-artery surgery, suggest that the 4G/5G polymorphism modulates basal PAI-1 concentrations and, as a consequence, the acute-phase levels of PAI-1. In these patients, postoperative PAI-1 concentrations appear to associate with length of stay in hospital, independently of other acute-phase changes.

P3504 The p22 phox gene polymorphism and altered coronary endothelial dependent vasodilator capacity

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Oxidative stress in the vasculature induced by .O2- has been implicated in the pathogenesis of CAD. The sources of .O2- in the vasculature are diverse and include VSMCs, endothelial cells, and macrophages. C24T2T p22phox NADH/NADPH oxidase polymorphism result in substitution of Tyr for His residue 72 which might may modulate enzyme activity by affecting heme binding. Recent data suggest that the CYBA 242T allele is associated with the increased progression of coronary disease.

This study was designed to detect the association between C242T polymorphism of the p22phox gene and the endothelium-dependent vasodilator capacity of human coronary arteries through the assessment of endothelium-mediated flow-dependent dilation and nitroglycerin, which is endothelium-independent.

Methods and Results: NADH/DAPH oxidase p22 phox polymorphism was determined; in 80 patients; by restriction fragment length polymorphism (RFLP). The vasodilator function of the epicardial arteries were assessed by endothelium-mediated flow-dependent dilation and nitroglycerin, which is endothelium-independent. A significant blunted endothelium-dependent dilator response was found in carriers of the CC genotype of the C242T P22 phox polymorphism (n=37) (12.0+ 8.9 luminal area change Vs 16.9+9.7 P=0.007), which was by multivariate analysis, independent of other risk factors or atherosclerosis itself. Carriers of p22 phox CC genotype show also a trend towards decreased endothelium-independent dilation.

Conclusion: From the present study it could be concluded that, C242T polymorphism of the p22 phox gene is an important determinant of coronary endothelial vasodilator function that is independent of the presence or absence of atherosclerotic disease, as well as coronary risk factors.

P3505 Not the atherosclerotic burden nor progression of atherosclerosis explain the cardiac event rate in relation to the E/D298 ecNOS polymorphism

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Nitric oxide (NO) plays a central role in endothelium-dependent dilatation of coronary arteries. Endothelial constitutive nitric oxide synthase (ecNOS) is the key enzyme in determining basal vascular wall NO production. The E/D298 polymorphism in the gene coding for ecNOS has been associated with an increased risk for myocardial infarction (MI). We investigated the impact of this ecNOS polymorphism on progression of atherosclerosis and cardiovascular events in patients with coronary artery disease (CAD) and compared the frequency distribution to a sample of the general population.

Methods: Patients were enrolled in the REGRESS trial which studied the impact of pravastatin therapy on CAD. Progression of atherosclerosis was determined using quantitative coronary angiography measuring changes in mean segment diameter (MSD) and minimum obstruction diameter (MOD) at baseline and after two years. Controls without known CAD matched for gender and age were taken from the general population. A total of 755 and 574 subjects were genotyped in the patient and reference group respectively.

Results: The rare allele (D) was present in 38.9% (95%CI 36.0%-41.7%) of the normal population. The preliminary data show that the genotype distribution differed significantly between subjects with and without CAD (EE and ED vs DD: OR 1.55, 95%CI 1.12-2.14). Within the CAD group, patients with the EE genotype more often had a history of MI than patients with the DD genotype with heterozygotes having an intermediate risk: 51% vs 47% vs 32%, p=0.009. However, there was no relationship between genotypes and baseline atherosclerotic burden or progression of atherosclerosis (MSD/MOD) in either the placebo or the pravastatin group.

Conclusions: The ecNOS EE genotype is associated with previous MI in CAD patients. Furthermore, this genotype is associated with CAD compared to the general population. This phenomenon is most likely due to differences in vasoreactivity since differences in atherosclerotic burden and progression of coronary atherosclerosis were absent.

P3506 Angiotensin-converting enzyme gene polymorphism predicts the antiremodelling effects of spironolactone in chronic heart failure patients

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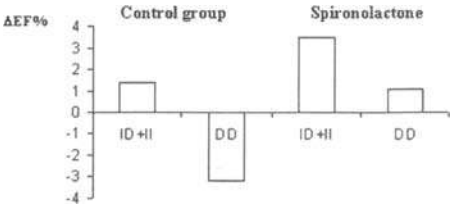
Purpose: In chronic heart failure (CHF) spironolactone (SP) improves survival; preliminary studies suggest an effect of this drug on left ventricular function. We aimed at assessing the contributory role of the angiotensin-converting enzyme (ACE) gene polymorphism on the antiremodeling effects of SP in CHF patients.

Methods: We randomised 89 CHF outpatients already on chronic treatment with ACE-inhibitors to SP, 25 mg od (n=47), or control group (n=42). Patients underwent genetic analysis and an echocardiographic evaluation at baseline and at 12 month follow-up, with measurement of left ventricular end-systolic volume (ESV) and ejection fraction (EF).

Results: At baseline, mean EF was 34±7%, and mean ESV 176±86 mL. Twenty-three patients (26% of total) had a DD genotype, 50 (56%) had an ID genotype and sixteen (18%) an II genotype. EF improved after SP treatment only in patients with the ID or II genotype, while it significantly decreased in patients with the DD genotype in the control group (ANOVA, p=0.03;figure 1). ESV at follow-up decreased compared with baseline after SP treatment only in patients with the ID or II genotypes, while it did not change in patients with the DD genotype (-26±31mL and 0±30 mL, respectively) and did not change in the control group (II+ID genotype: -3±35 mL, DD genotype: 1±41mL) (ANOVA, p=0.06).



Conclusions: SP significantly improves left ventricular EF and has a borderline effect on ESV only in the ID or II genotype. In patients with the DD genotype, SP administration prevents worsening of contractile function over time. Our results suggest that the effects observed during aldosterone antagonism in CHF patients might be at least in part genetically determined.

P3507 Associations of HFE gene polymorphisms with pre-transplant diagnosis and the development of cardiac transplant related vasculopathy

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Ischaemic heart disease (IHD) is the most common indication for heart transplantation. Abnormal iron metabolism has been postulated as an important risk factor for IHD. Hereditary haemochromatosis is a genetic disorder of iron overload common amongst people of Northern European descent. The gene encoding haemochromatosis, HFE, contains two polymorphic regions, C282Y and H63D which influence iron metabolism. We investigated the prevalence of these polymorphisms in a cohort of cardiac transplant recipients. We also related the genotypes to the development of cardiac transplant related coronary vasculopathy (CV). Genomic DNA from 143 heart transplant patients was analysed for C282Y and H63D polymorphisms using polymerase chain reaction and single strand conformational polymorphism. This was related to the pre-transplant diagnosis using contingency testing. CV was diagnosed at routine surveillance coronary angiography. Kaplan Meier survival analysis and log rank testing was used to assess for significance. We found that of patients transplanted for end-stage heart failure 56.6% had a preceding diagnosis IHD; 43.4% had non-ischaemic cardiomyopathy. H63D and C282Y homozygotes made up 80.4% and 85.3% of the cohort respectively. H63D heterozygotes were over-represented in the ischaemic relative to non-ischaemic groups; 25.9% vs. 11.2% ($p<0.05$). No difference was found in the prevalence of C282Y heterozygotes; 16.0% IHD vs. 12.9% non-IHD (p=NS). However, C282Y heterozygotes were much less likely to develop post-transplant CV; 46.0% vs. 81.0% disease free at 5 years for CC and CY respectively (p=0.035). H63D had no influence on CV development. To conclude, heterozygosity for H63D may be a risk factor for the development of end-stage ischaemic myocardial dysfunction requiring transplantation. Previous studies report conflicting evidence on the effects of C282Y and coronary artery disease, however, we found that heterozygosity for the C282Y polymorphism may be protective against cardiac transplant related coronary vasculopathy.

P3508 A deletion in the transcriptional activator EYA4 leads to dilated cardiomyopathy with sensorineural hearing loss

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25% of Dilated Cardiomyopathies are familial. The few gene defects identified so far, have led to the hypothesis that Dilated Cardiomyopathy is a disease of the cytoskeleton. We report for the first time about a mutation in a transcription factor (EYA4), which leads to a dilated cardiomyopathy accompanied by sensorineural hearing loss. A 5kb heterozygous deletion, which affects exons 9 and 10, presumably leads to a severe truncation of the EYA4 protein. This leads to the loss of the conserved EYA domain as well as a loss of a substantial part of the variable domain. In adult human tissue, EYA4 shows highest expression levels in cardiac and skeletal muscle. Recently described further carboxy-terminal truncating mutations in EYA4 lead to isolated Sensorineural Hearing Loss. We conclude, that the distal portion of the variable region contains a function, that is essential for the cardiac-specific activity of EYA4. EYA4 is one of the four vertebrate-specific orthologes of the Drosophila gene "eyes absent". A loss-of-function mutation in Drosophila eyes absent leads to programmed cell death of ocular precursor cells. As mutations in eyes absent lead to programmed cell death, we hypothesize that mutations in human EYA4 cause Dilated Cardiomyopathy and Sensorineural Hearing Loss through an impairment of apoptotic control.

GENE EXPRESSION

P3509 Differences in collagen I and III expression in atrial tissue of patients with atrial fibrillation with and without mitral valve disease

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Background: Collagen I and III, major components of the extracellular matrix, are increased in fibrotic tissues. Atrial fibrillation (AF) is a progressive disease associated with increased atrial fibrosis. AF usually turns paroxysmal (PAF) to chronic (CAF) with time. Histologically, most extensive atrial fibrosis could be shown in patients (pts.) with mitral valve disease (MVD) and CAF. We therefore postulated that atrial tissue expresses more collagen I and III in MVD than in lone AF. Additionally there should be lower levels of collagen I and III in PAF compared to CAF.
Methods and Results: Atrial tissue samples of pts. with lone AF (group I, n=47, 26 PAF, 21 CAF) and pts. with MVD (group II, n=44, 8 PAF, 31 CAF, 5 SR controls) were obtained during cardiac surgery for AF and/or MVD. Collagen I and III mRNA levels were measured by quantitative PCR (light cycler), protein levels by Western blotting techniques. Collagen I and III mRNA (26,6 (range 3,4-92,2) vs. 57,4 (range 4,9-175,0) and 10,3 (range 0,16-51,8) vs. 17,3 (range 0,3-97,8), respectively) and protein levels (0,6 (range 0,1-1,0) vs. 0,95 (range 0,4-1,5) and 1,2 (range 0,1-7,7) vs. 6,1 (range 0,1-49,0), respectively) were lower in group I but these differences were not statistically significant. Interestingly there were no differences between PAF and CAF pts. of group I and group II. Control pts. of group II express less collagen I and III mRNA and protein, although differences were also not statistically significant. Pts. with lone AF exhibit about the same levels of collagen I and III as pts. with MVD and SR.
Conclusions: Collagen I and III mRNA and protein levels are elevated in pts. with MVD as compared to lone AF. Since there was a similar degree of enhanced collagen expression in PAF and CAF, we conclude that fibrosis precedes AF. Further studies are needed to correlate these data to the histological degree of fibrosis.

P3510 BMP-10 is required for embryonic heart function

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Recently we identified a novel member of the TGF-b family, BMP-10 which is expressed exclusively in the trabeculated component of the developing mouse ventricle, beginning at d 9.0 p.c.
Shortly after formation of a single heart tube at approximately d 8.5 p.c. in the mouse the myocardium starts to differentiate into an outer compact myocardial layer and an inner spongy zone, the trabeculated myocardial layer. The function of this transient structure, the trabeculae, is presumably the maintenance of sufficient oxygenation and nutrient supply to the growing myocardium prior to the development of coronary arteries. During subsequent development, trabeculae are thought to coalesce, thereby forming the muscular portion of the interventricular septum and papillary muscles. Other observations demonstrated that the conduction rate is higher in trabeculae compared to compact myocardium. This was supported by the finding that connexin 40 and connexin 45 are more abundantly expressed in the trabeculae. Based on those and additional studies of gene expression patterns in the developing ventricles as well as on genetic studies, Moorman et al. suggest that the ventricular conduction system originates from the trabecular ventricular component.
We could show that after the initial expression of BMP-10 in the trabeculae BMP-10 expression changes during later development. After d 14.5 p.c. expression in the ventricle decreases and at the same time expression in the atrium increases. In the adult heart, BMP-10 expression is restricted to a small region in the right atrium containing the sino-atrial node. We further demonstrate that a null mutation of the heart specific BMP-10 gene results in a failure of the developing heart to trabeculate, leading to embryonic lethality caused by insufficient cardiac function. Taken together, these data suggest that BMP-10 might have a unique role during embryonic heart formation and, possibly, maintenance of the mature heart conduction system.

P3511 Promoter-analysis of muscle LIM protein (MLP): organ specific regulation by Nkx-2.5 and MyoD

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Introduction: Muscle LIM Protein (MLP) is an adaptor protein of the cytoskeletal apparatus, expressed exclusively in myokardium and skeletal muscle. Recent data using knock-out experiments suggest that MLP interaction with cytoskeletal filaments is important for ventricular compliance, and a disturbance of MLP function could lead to cardiomyopathy. Data regarding the regulation of organ-specific expression of MLP are not known to date. We therefore cloned and analysed the promoter region of MLP in order to investigate the regulation of MLP expression and to identify specific transcription factors.
Results: Cloning of a 3000 bp sequence upstream of the first exon (identified by 5'RACE) of the MLP genom into a luciferase expression plasmid resulted in a 40x increase in luciferase activity after transfection in 10T1/2-fibroblasts (mesnchymal precursor cells) and in C2C12 myoblasts compared to empty plasmid control, suggesting that the cloned sequence contained the putative MLP promoter region. Using deletion constructs the minimal promoter sequence could be narrowed to a -112/68 bp region; in shorter constructs luciferase activity was abolished. To identify regulatory transcription factors involved in striated muscle differentiation we performed cotransfection experiments with Nkx2.5 and Tbx, both being expressed during heart development, as well as with MyoD and Myogenin, expressed during skeletal myocyte differentiation. Whereas Tbx and Myogenin did not significantly affect MLP promoter activity, both Nkx2.5 and MyoD lead to a 8 to 10fold increase in promoter activity when cotransfected with MLP promoter, suggesting an important regulatory role for both transcription factors in MLP expression. To support this result we established a stable MyoD-expressing 10T1/2 cell line, which spontaneously forms myotubes; in these cells overexpression of MyoD was sufficient to switch on MLP expression, as shown by RT-PCR. Alternatively, overexpression of Nkx2.5 in 10T1/2 fibroblasts using an adenoviral construct could again induce MLP expression.
Summary: Our promoter analysis and overexpression experiments identified Nkx2.5 and MyoD as positive regulators of MLP expression. Since both transcription factors are expressed in an organ-specific manner, it can be argued that Nkx2.5 regulates MLP expression in heart, whereas MyoD induces MLP expression in skeletal muscle, at least during myocyte differentiation.

P3512 Endothelin and isoprenaline co-stimulation causes contractile failure in engineered heart tissue which is partially reversed by MEK inhibition

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Background: Progression of heart failure is due in large part to activation of neurohormonal systems like the endothelin- (ET) and the sympathetic nervous system. ET-1- and catecholamine-evoked signaling decisively involves the MEK-ERK-pathway and is implicated in key pathological processes. We hypothesized that MEK inhibition could prevent development of contractile dysfunction following combined ET-1 and isoprenaline (ISO) stimulation in engineered rat heart tissue (EHT).
Methods and Results: EHTs reconstituted from neonatal rat cardiac myocytes were cultured in serum containing medium for 6 days and treated with ET-1 (10 nM) + ISO (10 nM) for additional 5 days in the presence or absence of the MEK-Inhibitor U0126 (10 μM, n=15 each group). Isometric force of contraction (FOC) was measured under basal conditions and with increasing concentrations of calcium (0.4-2.8 mM) and ISO (0.1-1000 nM). ET-1+ISO treated EHTs showed a significantly diminished increase in FOC (delta FOC) in response to ISO (0.17±0.02 vs. 0.38±0.04 mN, $p<0.05$). Moreover, contraction (T1, 73.1±3.0 vs. 54.8±2.0 ms, $p<0.05$) and relaxation times (T2, 89.8±4.1 vs. 62.8±2.4 ms, $p<0.05$) were significantly prolonged. Effects of ET-1+ISO were partially reversed by U0126, resulting in an increased delta FOC in response to ISO (0.23±0.02 vs. 0.17±0.02 mN $p<0.05$) and normalization of T1 (61.5±1.9 vs. 73.1±3.0 ms, $p<0.05$) and T2 (75.1±3.3 vs. 89.8±4.1 ms, $p<0.05$). U0126 significantly decreased rate of protein synthesis by 18%, as assessed by 14C-phenylalanine incorporation. However, cardiac myocyte phenotype, investigated by immunohistochemical staining of sarcomeric actinin, did not differ between treatment and control groups.
Conclusions: ET-1+ISO treatment caused contractile dysfunction in EHTs suggesting that coactivation of the ET and sympathetic nervous system could play an important role in the progression of heart failure. MEK inhibition with U0126 partially reversed contractile dysfunction and decreased protein synthesis in the EHT model. These data support a role for MEK/ERK in pathological cell signaling.

P3513 Efficient gene transfer in 24 h Langendorff-perfused neonatal rat hearts

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After completion of the human genome project there is increasing need for valid, trustworthy and simple screening systems for the functional analysis of these genes. In our study we demonstrate that it is possible to perfuse isolated neonatal rat hearts for >24 h and perform an efficient adenoviral gene transfer. We developed a modified recirculating Langendorff-system with constant flow (1 ml/min) and monitored perfusion pressure, force and frequency of contraction. Optimisation of the serum-free medium allowed an perfusion for up to 48 h with constant pressure. The weight of the native hearts was 35.2±1.2 and after 24 h 36.6±2.8 mg/g bodyweight, the weight of lyophilised native hearts 19.5±0.2% that of 24 h perfused 17.4±0.6% of wet weight (n=12 and 10, $p<0.05$). This suggests 10% oedema, a result that was confirmed histologically by H&E stained paraffin sections.
After mounting the hearts and 3 h of equilibration, function was measured under basal conditions and after perfusion with isoprenaline (0.1 μM). This procedure was repeated after 24 h in the same way (n=13). Results are shown in table 1.

Table 1: Contractile parameters (n=13)

	Frequency [bpm]	Force of contraction [mN]	Time of relaxation [ms]	Velocity of relaxation [N/s]
3 h Medium	130±14	2.1±0.4	125±5	28±5
3 h Isoprenaline	168±14	3.5±0.4	81±2	58±7
24 h Medium	131±10	4.3±0.5	137±5	48±5
24 h Isoprenaline	155±11	5.7±0.6	95±5	87±10

When hearts were perfused with recombinant, replication deficient adenovirus encoding beta-galactosidase or the green fluorescent protein at a moderate dose (200 mio biologically active virus), transfection efficiency reached 30-60%. The gene transfer did not affect contractile parameters, indicating lack of virus toxicity. In summary, we have developed a new in vitro model that allows to study functional consequences of transient gene transfer on contractile force under well defined conditions in the intact heart.

ANIMAL MODELS IN ATHEROSCLEROSIS

P3514 Increased atherosclerosis in LDL receptor-null mice lacking the CC-chemokine receptor 4

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Immunologic and inflammatory responses play a crucial role in the development of atherosclerosis. Chemokines are a superfamily of small proteins involved both in routine leukocyte trafficking and in the activation and recruitement of specific cell populations to sites of inflammation and infection. CC-chemokine receptor 4 (CCR4), a high affinity receptor for the CC chemokines macrophage-derived chemokine (MDC) and thymus and activation-regulated chemokine (TARC), is expressed in the thymus and spleen, and also by peripheral blood T lymphocytes, monocytes, macrophages, platelets, and basophils. Recent studies have demonstrated a key role for CCR4 in lipopolysaccharide-induced endotoxic shock, but little is known on the role of this chemokine receptor in other inflammatory diseases. We have observed CCR4 expression in human atherosclerotic lesions. The purpose of this study was to examine the role of CCR4 in the development of atherosclerosis in vivo.
Atherosclerosis-susceptible LDL receptor-deficient mice were intercrossed with CCR4-deficient mice. Male double (CCR4-/-LDLR-/-) and single (LDLR-/-) knockout mice of 12 weeks old (n=6 per group) were fed a cholesterol-rich diet (1.25%) for 14 weeks. Atherosclerotic lesions were measured by computer image analysis measuring the extent of sudanophilic lesions within the thoraco-abdominal aorta and aortic root. Increase in serum lipid profiles (total cholesterol, triglycerides) did not differ between both groups.
The progression of atherosclerosis was significantly increased in the thoraco-abdominal aorta and aortic root of CCR4-/-LDLR-/- double knockout mice as compared to controls (LDLR-/- mice). For the thoraco-abdominal aorta, the lipid deposition was 21.3±4.5% and 11.2±2.2% for CCR4-/-LDLR-/- and LDLR-/- mice, respectively (mean±SEM, $p<0.05$). Similar results were obtained in aortic root analysis.
To our knowledge, this is the first demonstration that blocking a chemokine pathway increases the progression of atherosclerosis in vivo. Our results might point to a beneficial effect of the recruitement of a specific subset of inflammatory cells in the early phase of atherogenesis. This unexpected role for CCR4 in the development of artherosclerosis underlines the complexity of cellular interactions leading to this common disease.

P3515 The nitric oxide donor molsidomine favours features of atherosclerotic plaque stability during cholesterol lowering in rabbits

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Atherosclerotic plaques with an unstable phenotype are characterized by a thin fibrous cap containing numerous macrophage-derived foam cells and few smooth muscle cells (SMC). A treatment decreasing the number of macrophages and/or increasing the number of SMC might favour plaque stabilization. Therefore, we investigated in the aorta of cholesterol-fed rabbits (0.3% cholesterol, 20 weeks) the effect of 4 weeks cholesterol withdrawal as such and in combination with the nitric oxide (NO) donor molsidomine (0.1 or 1 mg kg-1 day-1) on atherosclerotic plaque size and on macrophage and SMC content using (immuno)histochemical techniques. We also studied superoxide production (lucigenin assay) and the expression of extracellular superoxide dismutase (ecSOD) mRNA (quantitative reverse transcription-PCR), respectively.
Cholesterol treatment led to atherosclerotic plaque formation in the aorta, an increase in superoxide production, and a decrease in ecSOD mRNA as compared to normal aortas. Cholesterol withdrawal alone led to the formation of a thin subendothelial macrophage-free layer and significantly reduced both vascular cell adhesion molecule-1 (VCAM-1) expression and cell replication in the luminal part of the plaque. It did not affect plaque area, apoptosis, superoxide production, and ecSOD mRNA expression. Treatment with molsidomine (1 mg kg-1 day-1) during the cholesterol withdrawal period increased the thickness of the subendothelial macrophage-free layer consisting of SMC, and resulted in a normalisation of both the superoxide production and ecSOD mRNA expression by the aorta.
The latter findings demonstrate that cholesterol lowering combined with molsidomine treatment increases features of stable atherosclerotic plaques.
[1]

P3516 Angiotensin II accelerated atherosclerosis is attenuated in osteopontin deficient mice

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Osteopontin (OPN) is large acidic phosphoprotein and acts through its arginine-glycine-aspartate (RGD) tripeptide integrin binding motif as an adhesion substrate and migration stimulus. These interactions with integrins result in activation of cell signaling pathways and regulation of gene expression. Angiotensin II (AII) is a potent inducer of OPN in the atherosclerotic vessel wall and overexpression of OPN has been identified in atherosclerotic lesions. We therefore hypothesized that OPN may play a key role in early and late changes associated with the development and progression of AII accelerated atherosclerosis. To test this hypothesis we bred OPN-/- with ApoE-/- mice to develop heterozygote ApoE-/-OPN+/- and homozygote ApoE-/-OPN-/- double knock-out mice. Three month old male ApoE-/-OPN+/- and ApoE-/-OPN-/- mice and ApoE-/-OPN+/+ littermate controls were infused with 2.5 μg/kg/min AII for 4 weeks. All 3 groups developed marked hypertension (systolic 160 mmHG vs. 100 mmHG in control animals). En face analysis of the thoracic aorta revealed a significant 65% decrease in atherosclerotic lesions in OPN deficient mice compared to ApoE-/-OPN+/+ littermate control mice (ApoE-/-OPN+/- 5.3%, n=9; ApoE-/-OPN-/- 5.1%, n=6; ApoE-/-OPN+/+ 15.3%, n=4). Real time RT-PCR confirmed that OPN mRNA expression was decreased by 50% in ApoE-/-OPN+/- mice and not detectable in ApoE-/-OPN-/- mice. Lipid profiles were similar in the 3 groups. Peritoneal macrophages from OPN deficient mice exhibited an impaired chemotactic response in transwell migration assays which could contribute to the diminished atherosclerosis observed in the OPN deficient mice. These data suggest that OPN is an important proatherogenic factor in the vessel wall. Approaches designed to inhibit OPN expression and/or adhesion in vasculature may provide a novel therapeutic strategy against atherosclerosis.

P3517 Increased vascular cell apoptosis and proliferation after balloon injury in p53 null mice

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A disequilibrium between vascular cell death and proliferation is a prominent feature in the response to vascular injury. A phase of marked medial apoptosis is known to initiate the process of balloon-induced lesion formation in large animals. At the molecular level, p53 is a known mediator of apoptosis and cell cycle arrest that is induced by DNA damage and has been associated with restenosis. However, a cause-effect between p53 and balloon-induced lesion formation is still unknown. We tested the hypothesis whether the lack of p53 would decrease apoptosis and enhance proliferation after balloon injury.
Balloon distension injury was performed in the non-dissected portion of the left proximal common carotid artery of p53-/- and wild-type C57Bl/6 (WT) male mice weighing 22.5 to 24.5g. Serial cross sections of the dilated segment of the carotid artery were obtained 3h, 1, 7 and 28d after balloon injury (n>7 for each group, mean±SD). Cellularity was determined by chromatin staining (DAPI) and DNA synthesis was assessed by BrdU labeling index (BrdU-I). Cell death and apoptosis were characterized by the typical nuclear morphology that was confirmed by TUNEL and active caspase-3 staining. Medial cellularity decreased early, then increased at d7 and 28 in a similar fashion in both strains. However, at 1d post injury, total medial cell count was lower in p53 -/- than in WT mice (38±20 vs. 59±13, $p<0.05$). Indeed, counts of cell death were higher in p53-/- than in WT mice at 3h (17±6 vs. 10±5, $p<0.05$), 1d (10±7 vs. 4±4, $p<0.05$), 7d (9±5 vs. 5±4, $p<0.05$) and 28d (8±8 vs. 1±1, $p<0.001$) post injury. On the other side, medial proliferation (BrdU-I) was also higher in p53 -/- mice at 7d (8±6 vs. 5±4, NS) and at 28d (0.9±1.2 vs. 0.6±1.0, $p<0.05$). Intima analysis revealed that its cellularity decreased sharply 3h post injury in both strains (4±2 vs. 5±3, NS), then increased more in p53 null mice at 7 (149±92 vs. 101±63, NS) and 28d (83±43 vs. 46±7, $p<0.001$). These findings were paralleled with an increased intimal proliferation rate in p53 null mice at 7d (11±10 vs. 4±3, $p<0.05$) that leveled off and became similar in both strains at day 28. Lumen areas and intima/media ratio were not different between the strains.
p53 null mice show a higher rate of cell apoptosis and proliferation after carotid balloon injury. The paradoxical increase in cell death in p53 -/- mice suggests a compensatory activation of p53-independent apoptosis pathways in these animals. The increase in cell proliferation in p53 knockout mice is likely due to the lack of cell cycle arrest mediated via p53.

P3518 Omapatrilat accelerates reendothelialisation and prevents fatty streak deposit in a novel model of mouse carotid injury

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Background: The importance of endothelial integrity was initially demonstrated by the facilitation of atherosclerotic lesion development in hypercholesterolemic animals models endothelial injury. We have previously shown that omapatrilat prevents spontaneous fatty streak deposit at the root of the aorta. We have evaluated the effect of omapatrilat, a dual ACE and NEP inhibitor, on the acceleration of reendothelialization in wild-type mice and the development of fatty streak in apolipoprotein E (apoE)-deficient mice after arterial injury.
Methods: Firstly, 2 groups of six male wild-type mice were given either placebo or omapatrilat 100 mg/kg/day. Reendothelialization was evaluated by staining the denuded areas with Evans blue. Secondly, 2 groups of six male apoE-deficient mice were given either placebo or omapatrilat 100 mg/kg per day after carotid injury for 3 months. The evaluation of fatty streak deposit was evaluated using red oil staining.
Results: 3 days after arterial injury, in wild-type mice treated with omapatrilat in mice demonstrated placebo accelerated reedothelialization compared to placebo (% of area remaining deendothelialized = 38.8 ± 1.5, vs = 46.9 ± 2, $p<0.005$). Placebo-treated apoE-deficient mice developed fatty streak deposit at the site of injured carotid, whereas the uninjured controlateral carotid artery demonstrated no lesion. In contrast, ApoE-deficient mice treated with omapatrilat had almost no fatty streak deposit 3 months after arterial injury.
Conclusion: Omapatrilat accelerates reendothelialization after carotid arterial injury in wild-type mice and protect the apoE-deficient mice from fatty streak deposit after arterial injury. The benefit of the dual ACE and NEP inhibition should be considered in the prevention of atherosclerosis after endoluminal angioplasty.

DOPPLER ECHOCARDIOGRAPHY

P3519 Comparison between parameters of diastolic function derived from conventional Doppler echocardiography and from Doppler tissue imaging

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Background: Measurement of left ventricular flow propagation velocity (LV FPV) is a useful noninvasive estimate of Tau. Doppler tissue imaging (DTI) seems a promising new echocardiographic approach of diastolic function.
Methods: We studied 54 pts (50±17 yrs, 16 nl pts, 29 pts with idiopathic DCM, and 9 pts with primary pulmonary hypertension) and recorded from apical 4C view 1) LV FPV with color M-mode echocardiography, 2) mitral flow (mit) with conventional Doppler, 3) septal (sep) and lateral (lat) wall motion with pulsed Doppler tissue imaging (DTI). We tried to correlate color M-mode LV FPV (mean value: 46.1±16.7 cm/s), that is well correlated with Tau, with the following parameters: maximal velocity of mit, sep and lat E waves; mit, sep, and lat E/A ratio; LV, sep, and lat myocardial performance index (MPI). LV MPI is defined as the ratio of the sum of isovolumic contraction and relaxation times to ejection time, and is an index of global function. We applied the same formula to DTI derived sep and lat time intervals.
Results: see table.

Correlations with LV FPV

	mean±SD	r value	p value
age	50±17	-0.487	0.002
mit E (cm/s)	69.5±22.6	0.579	0.000
sep E (cm/s)	7.7±3.3	0.545	0.000
lat E (cm/s)	10.5±4.9	0.659	0.000
mit E/A	1.4±1.0	0.318	ns
sep E/A	1.1±0.6	0.609	0.000
lat E/A	1.5±1.1	0.505	0.004
LV MPI	0.59±0.24	-0.468	0.003
sep MPI	0.92±0.62	-0.500	0.002
lat MPI	1.5±1.1	-0.125	ns

Conclusion: Our study shows interesting correlations between pulsed DTI parameters of diastolic or global function and LV FPV, suggesting further correlations with Tau.

P3520 Detection of a pseudonormal mitral inflow pattern using Doppler myocardial imaging

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Background: Impaired relaxation can be masked by elevated filling pressures, resulting in a pseudonormal mitral inflow pattern. Aim of the study was to assess the ability of Doppler myocardial imaging (DMI) - derived parameters to improve the noninvasive diagnosis of pseudonormalization.
Methods: 83 consecutive patients with a normal transmitral Doppler profile (E/A > 1) scheduled for coronary angiography underwent DMI and left heart catheterization. Peak transmitral velocities were determined at rest (E, A) and during the strain phase of a Valsalva maneuver (Ev, Av). Propagation velocity of the early mitral inflow (Vp) was measured by color M-mode. Early diastolic peak velocities of lateral mitral annulus (E') and the peak diastolic myocardial velocity gradient of the posterior basal wall (MVG) were obtained by DMI. Myocardial relaxation time (MyoRT) was calculated between aortic valve closure and the early diastolic myocardial velocity peak of the posterior basal wall by DMI. The left ventricular end-diastolic pressure (LVEDP) and ejection fraction (EF) were determined invasively.
Results: Pseudonormalization, defined as LVEDP > 14 mm Hg and E/A > 1, was found in 46 patients (LVEDP 21 ± 7 mm Hg, EF 62 ± 15%, E/A 1.4 ± 0.5), while 37 patients served as a control group (LVEDP 7 ± 2 mm Hg, EF 71 ± 8%, E/A 1.4 ± 0.4). Parameters presenting significant differences between these 2 groups are summarized in the table, together with the coefficients of linear correlation with LVEDP and the values of AUC (area under the receiver-operating characteristic curve for the prediction of LVEDP > 14 mm Hg).

Parameters	Pseudonormalization	Control group	AUC (ROC-Curve)	r
Valsalva response	0.28 ± 0.28 *	0.14 ± 0.22	0.667 *	0.43 **
E/E'	14.2 ± 6.1 **	9.9 ± 2.9	0.724 **	0.45 **
MyoRT (ms)	118 ± 31 **	82 ± 17	0.738 **	0.45 **
E/Vp	1.8 ± 0.8 **	1.2 ± 0.5	0.751 **	0.39 **
MVG (1/s)	-2.5 ± 1.5 **	-4 ±1.7	0.775 **	0.45 **

Valsalva response = 1-(Ev/Av)/(E/A); r = coefficient of linear correlation with LVEDP; * $p < 0.05$; ** $p < 0.01$

Conclusions: 1) MVG had the highest predictive accuracy to identify elevated filling pressures. 2) Combined indexes MyoRT, E/Vp and E/E' are faster reliable alternatives superior to Valsalva maneuver for detecting a pseudonormal Doppler profile.

P3521 Dependence on venous return of diastolic left ventricular flow propagation and mitral annular velocities

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Background: The response of diastolic mitral flow to increased venous return due to leg lifting (LL) provides prognostic information in congestive heart failure patients. Recent studies in open chest coronary surgery patients explained these effects in terms of length dependent activation of cardiac muscle and contraction-relaxation coupling. Colour M-mode of mitral inflow and tissue Doppler imaging of mitral annular motion have been presented as relatively preload independent parameters. The present study analysed the response to LL of Doppler measurements in healthy subjects.
Methods and Results: Pulsed Doppler of left ventricular filling and outflow, colour M-mode of early left ventricular filling and mitral annular velocities were measured at baseline and during 45° LL (n=24).
LL resulted in increased stroke volume (69.1 ml ± 13.5 to 73.5 ml ± 13.5, P<0.01), left ventricular ejection time (286 ms ± 20 to 293 ms ± 18, P<0.01) and systolic annular velocity (6.8 cm/s ± 1.2 to 7.3 cm/s ± 1.1, P<0.01). LL induced an increase in peak early (E) mitral flow velocity (73.5 cm/s ± 12.9 to 80.3 cm/s ± 13.6, P<0.01), flow propagation (53.1 cm/s ± 10.2 to 59.2 cm/s ± 12.6, P<0.01) an E' diastolic annular velocity (10.8 cm/s ± 2.2 to 11.7 cm/s ± 2.0, P<0.01). There was a shortening of E wave deceleration time (178 ms ± 27 to 163 ms ± 27, P<0.01) and isovolumic relaxation time (76 ms ± 11 to 68 ms ± 10, P<0.01). Interobserver variability was low (mean of the difference for E was 0.3 cm/s ± 0.5).
Conclusions: LL enhanced systolic function according to Frank-Starling's law. The changes of diastolic function reflected the combination of elevated filling pressures and accelerated relaxation. Flow propagation and diastolic mitral annular velocities obviously were dependent on venous return.

P3522 Inadequacy of mitral flow propagation velocity assessed by color M-mode Doppler for differentiation of pseudonormal from normal left ventricular filling

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Background: Impaired diastolic LV function may be associated with a normal E/A ratio of mitral inflow in the presence of combined relaxation and compliance abnormalities. We sought to assess whether flow propagation velocity (vp) of early LV filling determined by color M-Mode Doppler may enable differentiation between such pseudonormal from normal velocity profiles. Methods: We studied 43 patients with marked LV hypertrophy due to hypertension and a normal mitral inflow E/A ratio as well as no valvular lesion. Fourty healthy persons served as control group. From PW Doppler registered LV filling profiles E, A, E/A, E acceleration and deceleration slopes as well as time intervals were measured. Flow propagation velocity vp was determined as the slope of the aliasing velocity from color M-Mode Doppler recordings oriented from the LV apex towards the tips of the mitral leaflets. Results: In the entire patient group with a pseudonormal filling pattern, vp was not significantly different from the control group, 73 ± 37 vs. 74 ± 32 cm/s. Only 5/43 patients showed a vp < 45 cm/s and all of them had a reduced systoliv LV function. Except for acceleration slope, which measured 997 ± 367 in patients with pseudonormalisation vs. 755 ± 260 cm/s^2 in normals, no significant differences were present for all other PW Doppler parameters between both groups. Conclusion: 1) Flow propagation velocity of early LV filling is frequently normal in patients with a pseudonormal mitral inflow profile and, thus, does not enable differentiation from normal filling patterns. 2) Reduced flow propagation is found in patients with impaired systolic LV function suggesting that ventricular suction is a major determinant of vp.

P3523 Pulsed-wave tissue Doppler echocardiography of various corners of mitral annulus in assessment of left ventricular diastolic function

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Background: Early diastolic mitral annulus (Em) velocity measured by pulsed wave tissue Doppler echocardiography (PW-TDE) has been referred to be a relatively preload independent parameter of left ventricular (LV) diastolic function. However, there are substantial differences among Em velocities measured on various corners of mitral annulus. Therefore, uniform cut-off values distinguishing normal and abnormal LV diastolic function are difficult to apply.
Aim of the study: To compare the sensitivity and the specificity of Em velocities measured on septal, lateral, posterior and anterior corner of mitral annulus by using receiver operating characteristics (ROC) curves analysis and to determine cut-off values for selected limit of 90% sensitivity.
Methods: Pulsed wave Doppler analysis of mitral inflow and pulmonary venous flow was performed in 69 patients (65% men, mean age 49±19 years). Patients were then classified into two groups: group N with normal LV filling pattern (n=35) and group I with impaired LV filling pattern (n=34). The latter included 23 subjects with impaired relaxation and 11 patients with pseudonormalized filling pattern. PW-TDE was performed on the septal, lateral, inferior and anterior corner of mitral annulus and peak Em velocities were measured. ROC curves of Em velocities were compared by assessing the areas under the curve (AUC) and 95% confidence intervals.
Results: Em velocities were significantly (p<0,001) lower in the group I compared to the group N. AUC of ROC curves were comparable on all four corners of mitral annulus ranging from 0,92 on the septal corner to 0,96 on the lateral corner. Cut-off values and specificities (for 90% sensitivity) were -0,09 m.s-1 and 89% on the septal corner, -0,12 m.s-1 and 94% on the lateral corner, -0,10 m.s-1 and 94% on the inferior corner and -0,11 m.s-1 and 91% on the anterior corner.
Conclusions: Values of Em velocity differ substantially according to the site of measurement. On all mitral annular corners the assessment of Em velocity allows detection of LV diastolic dysfunction with high and comparable sensitivity and specificity. However, different cut-off values should be used with the lowest value for the septal corner of annulus (-0,09 m.s-1) and the highest for the lateral corner (-0,12 m.s-1).

P3524 Evaluation of diastolic function of the left ventricle in white coat hypertension patients using tissue Doppler imaging

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Background The clinical significance of white coat hypertension (WCH) has been a subject of much debate. In this study we hypothesise that patients with WCH will have impaired diastolic function, similar to hypertensive patients with a family history of hypertension (FHT).
Methods Sixteen patients with WCH (mean age 36.25±11.3 years, mean daytime blood pressure 135/84 mmHg), and 13 FHT patients (mean age 37.6 ± 8.7 years, mean daytime blood pressure 146/94 mmHg), were compared with 14 controls (mean age 31.8 ± 6.9 years, mean daytime blood pressure 113/74 mmHg). From apical four chamber projections, the E wave velocity, E/A ratio, isovolumic relaxation time (IVRT), and deceleration time (DT), were measured from transmitral Doppler velocities. From apical long axis projections, (posterior mitral annulus), the peak systolic velocity (Sa), early (Ea) and late (Aa) diastolic velocities, the Ea/Aa ratio were measured with pulsed TDI. The E wave velocity corrected for the influence of relaxation as a less load dependent index (i.e., the E/Ea ratio) was also measured.
Results E, A, E/A transmitral velocities, were similar between WCH, FHT and controls. Similarly, there were no differences between Ea, Aa and Sa of WCH, FHT and controls. Only DT (WCH 176 ± 41 vs controls 142 ± 24 msec, P<.012, FHT 183 ± 36 vs controls 142 ± 24 msec, P<.002), and E/Ea (FHT 5.7 ± 1.3 vs WCH 4.7±.95 P<0.031) were higher in FHT compared with both, WCH and controls respectively.
Conclusion This study suggest that patients with WCH have normal diastolic function which distinguishes this group from patients with FHT. This distinction could have significant prognostic implications.

P3525 Adamantiades-Behcet's disease is associated with impaired aortic distensiblity and left ventricular diastolic function

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Adamantiades-Behcet's disease (ABD) is multisystem disorder characterized by vasculitis leading to vascular complications (VC) such as aneurysm formation, stroke, arterial or venous occlusive disease. Endomyocarial fibrosis has also been described in ABD. We investigated whether ABD is related with impaired aortic distensibility (AoD) and left ventricular (LV) function.

Methods: We studied 50 patients with ABD (age 38+11 years) and 20 normal controls by 2D, and Doppler Echocardiography. AoD was calculated using the formula 2 x (pulsatile change in aortic diameter)/[diastolic aortic diameter x (aortic pulse pressure)]. Thoracic aorta diameters (TAO-mm/m^2) were measured 3 cm above the aortic valve by 2D guided M-mode echocardiography and pulse pressure was obtained simultaneously by cuff sphygmomanometry. Isovolumic relaxation time (IVRT-ms), deceleration time (DT-ms) and flow propagation index (FPI-m/s) were measured to assess diastolic LV function. The duration of disease from diagnosis to time of examination and presence of VC were noted.

Results: All patients had normal systolic LV function. Patients and controls had similar age and atherosclerotic risk factor distribution. AoD and stiffness (cm^2 dyn(-1) 10^{-6}), IVRT and FPI were impaired in patients with ABD compared to controls (table). The duration of disease was related to low AoD and high TAO (r=- 0.48 and r=0.52, P<0.01) independently of age and risk factors. Patients with VC (n=19) had higher LV mass (g/m^2) left atrium (LA-mm/m^2)and DT than patients without (table). DT>190ms predicted VC with 83% sensitivity and 81% specificity (ROC curve area:81% (CI:65-97%)) independently of age and risk factors.

	Ao D	Ao stiffness	IVRT	FPI	Vascular complications	LV mass	LA	DT
Behcet (n=50)	0.79±0.5	53±38	85±13	0.42±0.1	Yes (n=18)	103±12	19±1	220±34
Controls (n=20)	2.0±0.9	15±6	70±15	0.69±0.3	No (n=32)	89±17	16±2	180±30
p	<0.01	<0.01	<0.01	<0.01	p	<0.01	<0.01	<0.01

Conclusion: ABD is related with impaired AoD possibly due to vasa vasorum vasulitis leading to increased Ao diameters as disease progresses in time. ABD is related with impaired diastolic LV function likely due to coronary vasculitis leading to endomyocardial fibrosis. Diastolic LV dysfunction is linked to presence of vascular complications implying the presence of a common pathophysiological pathway.

P3526 Do patients with heart failure and normal systolic function really have diastolic heart failure?

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Background: Diastolic heart failure (DHF), conventionally defined by exclusion (clinical heart failure [CHF] with normal LV systolic function), is reported to account for 30-50% of CHF in the community. We sought to use new echo-Doppler parameters to make a specific (rather than exclusive) diagnosis of isolated DHF among pts referred to a large tertiary echo center for assessment of LV function.

Methods: Between April 2000 and June 2001, 938 consecutive pts were referred for echo assessment of LV function. Pts with clinical CHF and normal LV systolic function, no wall motion abnormalities or valve disease, and no history of coronary artery disease were assessed for evidence of diastolic dysfunction based on transmitral and pulmonary vein flow. Impaired LV relaxation (IR) was defined by E/A<1 and E wave deceleration time (DT) >240msec. Pulmonary vein systolic (S), diastolic (D) and atrial reversal (A rev) velocities were used to differentiate pseudonormal (PN) filling (S/D<1 or A rev>35cm/s) in pts with normal E/A and DT who had LV hypertrophy or left atrial dilatation.

Results: Normal LV systolic function was present in 331 of 938 pts (35%). Fifty-three (27 male, age 72±11yrs) pts from this group (6% of referrals) met the inclusion criteria for a clinical diagnosis of DHF. Hypertension, and diabetes were present in 34 (64%) and 16 (30%) pts respectively. Twenty pts (38%) presented with acute CHF (19 admitted to hospital); 42 pts (79%) had chronic CHF symptoms. Diastolic dysfunction was confirmed by echo in 38 pts (72% of clinical DHF pts), of whom 27 pts had IR (E/A 0.75±0.16, DT 291±40 msec), 10 pts had PN filling (E/A 1.37±0.74, DT 190±42 msec), and 1 pt had restrictive filling. Diastolic function was normal in 13 pts and indeterminate in 2 pts. Diastolic dysfunction pts had increased LV septal thickness compared with pts with normal diastology (1.3±0.2 vs 1.1±0.2 cm, p=0.01). In comparison with pts with normal diastolic function, pts with PN filling had increased E velocity and E/A ratio (p<0.05 for both), and pts with IR had reduced E/A ratio (p<0.05) and prolonged DT (p<0.0001).

Conclusion: Isolated, clinically defined DHF is uncommon (6%) among pts referred for echo assessment of LV function at a tertiary center. However, echo evidence of diastolic dysfunction is present in the majority (72%) of these pts with clinically defined DHF. Most of these pts have impaired LV relaxation, but pseudonormal filling also accounts for a significant proportion (26%) of diastolic dysfunction in this population.

P3527 Subtle left ventricular systolic dysfunction detected by tissue Doppler is a diagnostic tool in heart failure with "preserved" systolic function

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Aims: To evaluate the diagnostic utility of tissue Doppler echocardiography to identify patients with heart failure in presence of preserved systolic function

Methods: We evaluated 80 patients with left ventricular ejection fraction (LVEF) >=50%, 29 of them with heart failure, defined as subject who meet Framingham diagnostic criteria (Group 1), and 51 normal subject (Group 2). LVEF was measured by cross sectional Simpson's method and myocardial velocities were obtained by pulsed tissue doppler (pTD) at the basal septum wall in 4-chamber view. Sensitivity (S), specificity (E) and predictive value, positive and negative (PPV and NPV), were determined and ROC curves were used to select the best values.

Results: Mean age of group 1 and 2 was 67.3±13 vs 51.1±20 years (p<0.001) and LVEF was 65.3±8.2 vs 59.7±6.7 (p=0.002), respectively. pDT values in group 1 and 2 were the followings: peak E 5.9±2.4 vs 10.5±4 cm/s; peak S 5.6±1.7 vs 8.2±1.5 cm/s; peak A 7.2±3.4 vs 9.5±2.5 cm/s; isovolumic myocardial relaxation time (IVRT) 162.4±39 vs 89.3±23.3 ms; and isovolumic myocardial contraction time (IVCT) 106.8±34 vs 69.1±17 ms (all p<0.001). The area under the ROC curve and the S, E, PPV and NPV are displayed in the table:

Variable	Area	Cut point	S (%)	E (%)	PPV (%)	NPV (%)
Peak E	0.85	7.15 cm/s	78.4	76.9	66.7	85.1
Peak A	0.70	7.25 cm/s	82.4	49.3	60.9	73.7
E/A ratio	0.65	0.75	68.6	55.6	50.0	72.9
Peak S	0.89	6.75 cm/s	88.2	80.0	79.3	88.2
IVRT	0.95	117.5 ms	86.3	93.1	79.4	95.7
IVCT	0.86	87.5 ms	84.3	72.4	72.4	84.3

Conclusion: pDT was a usefulness tool to diagnose heart failure in patients with preserved systolic function, and the most important parameters were IVRT (diastolic function) and peak S (systolic function). Thus, despite normal ejection fraction, subtle impairment of left ventricular systolic function is present in patients with diastolic heart failure and our findings suggest that these abnormalities may have an important role to identify that subjects.

P3528 Early detection by pulsed Doppler tissue imaging of diastolic but also systolic myocardial dysfunction after anthracycline chemotherapy

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Background: Anthracycline chemotherapy is the treatment for numerous malignant tumors despite a risk of cumulative chronic cardiotoxicity. We prospectively assessed the interest of pulsed Doppler Tissue Imaging (DTI) measurements for early detection of this cardiotoxicity.
Methods: We included 20 patients aged 38±10, without heart disease, who will undergo anthracycline treatment for breast cancer (n=11), lymphoma (n=5) or leukaemia (n=4). We performed two complete echocardiograms: one before the beginning of treatment and another one 6±4 months later. We recorded pulsed DTI spectrum of the basal segments of the posterior (Radial myocardial function (R)) and lateral (Longitudinal myocardial function (L)) left ventricular walls.
Results: For a doxorubicin cumulative dose of 227±91 mg/m^2, the left ventricular ejection fraction remained normal (71±8%). On mitral flow Doppler, there was an alteration of the relaxation: decrease of E wave velocity (65±12 cm/s vs 74±13 cm/s; p=0.04) and E/A ratio (1.34±0.28 vs 1.57±0.38; p=0.01). DTI study showed an alteration of the systolic (S) and early diastolic (Em) myocardial wave velocities, predominant for L. The decrease of S was significant for the lateral wall (table). The late diastolic myocardial velocity was unchanged.

	SL (cm/s)	SR (cm/s)	EmL (cm/s)	EmR (cm/s)
Before chemotherapy	12±2	9±2	17±3	14±3
After chemotherapy	11±3	8±2	14±3	12±3
p	0.02	0.07	0.01	0.02

DTI measurements before and after anthracycline chemotherapy

Conclusion: Pulsed DTI rather than usual Doppler echography detects early diastolic, but also systolic myocardial dysfunction, despite the absence of LVEF change in patients who undergo anthracycline chemotherapy.

P3529 Mitral color Doppler M-mode during dobutamine stress echocardiography: a marker of ischaemic myocardium

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Aim: The flow propagation velocity of early transmitral flow (Vp) determined by color Doppler M-mode was reported as a non-invasive index of global left ventricular relaxation, independent of loading or chronotropic ventricular changes. Vp determination could help dobutamine stress echocardiography (DSE) to recognize more objectively ischemic myocardium.
Methods: Forty-six consecutive patients (pts), mean age 63 ± 6 years, with known or suspected coronary artery disease underwent DSE. Vp was determined as the slope of the isovelocity line from mitral plane to 4 cm apically into the left ventricle. Vp was recorded at a sweep rate of 100 mm/s and calculated off-line at each step of DSE. Pts with significant arrhythmias, mitral or aortic valve disease and diastolic restrictive pattern were excluded. Coronary angiography (CAG) was performed within 3 months of DSE. A coronary stenosis was defined significant if >70% of lumen diameter of epicardial coronaries (>50% of left main coronary artery).
Results: Mean Vp at rest, low, peak dose of dobutamine and recovery of pts with ischemic and non-ischemic DSE are shown on the table. Peak dose Vp (cut-off <31 cm/s) predicted coronary artery disease: agreement 78%, kappa 0.35. During DSE Vp changes correlated to ischemic wall motion patterns and biphasic Vp correlated to biphasic wall motion changes (r = 0.85). In some cases of myocardial ischemia the dobutamine-induced reduction of Vp at peak test was on-line eye-recognizable.

(cm/s)	Rest	Low dose	Peak dose	Recovery
(a) Non-ischemic pts	60±16	73±20	73±15	63±18
(b) Ischemic pts	57±14	71±19	32±11*	51±17

* p <0.01 between (a) and (b).

Conclusions: In pts with known or suspected coronary artery disease, dobutamine-induced Vp reduction appears an accurate marker of coronary artery stenosis. Vp reduction reflects the slowed ventricular relaxation induced by ischemia. Vp change allows quantitation of myocardial ischemia and in same cases also on-line eye-recognition of myocardial ischemia. Vp patterns during DSE partially parallel wall motion patterns.

P3530 Assessment of regional diastolic left atrial function by pulsed-wave tissue Doppler imaging

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Background: Tissue Doppler imaging (TDI) allows to study the regional diastolic function in several clinical settings. Nevertheless, quantitative TDI of the LA has been poor studied. The aim of this study was to assess the regional diastolic function of the LA by TDI in a cohort of healthy subjects. Furthermore, we studied the relationship between the LA TDI patterns and the transmitral and pulmonary vein flows.
Methods: Ninety subjects (50 women) mean age 48±22 years (range 9-75 years)were studied. All subjects were examined using the four- chamber apical view. The lateral wall of the LA was divided in three erial segments (basal, medium and distal). The sample volume was placed in the center of these consecutives segments to be analized. In each atrial segment, the following measurements were acquired: Vs, Ve, Va and e/a ratio. TDI measurements were expresed as average values of 3 consecutive beats in each segment. To avoid the possible effect of the age on the actual measures, the study population was divided in two groups: group I (age<45 years) and group II (age>45 years). Transmitral and pulmonary venous flow velocities were obtained.
Results: TDI velocities in each group of age are shown in the table. The youngest subjects (group I) exhibit a pattern with high e wave and e/a ratio>1. With the age (group II), the relationship e/a it is made smaller than 1. It was not observed differences in the Vs between both age groups (13.5 ± 3.9 group I vs 13.1 ± 5.4 cm/sec group II; p=0.59). There were no relationship between the pulmonary venous flow velocities and those of LA TDI. On the contrary, a significant correlation was observed among the transmitral flow pattern and the LA TDI tracing (Kappa=0.584; p>0.0001). This relationship stays constant in all the age groups.

TDI velocities

Left Atrial TDI	s wave (cm/s)	e wave (cm/s)	a wave (cm/s)	e/a ratio
Group I	13.5 ± 3.9	22.6 ± 6.4	15.2 ± 6.1	> 1 (88%)
Group II	13.1 ± 5.4	10.5 ± 6.1	19.6 ± 7.9	< 1 (86.5%)
p value	0.59	P < 0.0001	P <0.03	P < 0.0001

TDI velocities in each group of age.

Conclusions: LA shows a similar TDI pattern to that of the left ventricle with a systolic wave and two diastolic waves. A narrow correlation of the diastolic patterns exists between the transmitral flow obtained by conventional pulsed Doppler, and those of the LA obtained by TDI.

P3531 The TEI index as a predictor of in-hospital cardiac events in patients with myocardial infarction

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Objective: Recently, an easily measured Doppler index of global myocardial performance (TEI index), defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time, has been proposed as a sensitive marker of cardiac dysfunction in patients with myocardial infarction (AMI). However, data regarding the ability of the TEI index to predict in-hospital cardiac events in AMI are lacking.
Methods: A complete two-dimensional and Doppler echocardiographic examination was performed within 24 h of arrival at the coronary care unit in 96 patients (81 men and 15 women; mean age 58 ± 9 years) with first AMI (42 anterior, 47 inferior and 7 lateral). Patients were divided a posteriori into 2 groups according to their in-hospital course: group 1 comprised 21 patients with a complicated in-hospital course (death, heart failure, arrhythmias or post-AMI angina) and group 2 comprised 75 patients with an uneventful course.
Results: Cardiovascular risk factors and conventional parameters of diastolic function were similar between the 2 groups. In complicated patients, the Killip class was higher (p = 0.0001), the wall motion score index and the left ventricular systolic volume were significantly increased compared with patients without events (1.84 ± 0.27 vs 1.52 ± 0.30, p = 0.0001; and 66 ± 29 ml vs 47 ± 21 ml, p = 0.001), whereas the ejection fraction was reduced (40 ± 10% vs 52 ± 10%, p = 0.0001). The mean value of the TEI index was significantly higher in patients with cardiac events than in those wihout events (0.65 ± 0.20 vs 0.43 ± 0.16, p = 0.0001), due to a prolonged isovolumetric contraction time (72 ± 37 msec vs 44 ± 27 msec, p = 0.001) and shortened ejection time (245 ± 35 msec vs 265 ± 26 msec, p = 0.007). A Tei index > 0.47 showed a sensitivity of 90%, specificity of 71% and a negative predictive value of 96% for identifying subjects with events. By multivariate logistic regression analysis, the TEI index (OR 13.5, 95% CI 2.5-71.3, p = 0.002) remained independently predictive of in-hospital cardiac events.
Conclusion: The present data suggest that in the acute phase of AMI, the TEI index is a strong predictor of in-hospital cardiac events.

P3532 The TEI index as a predictor of short term outcome in ischaemic cardiomyopathy

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The Carvedilol Hibernation Reversible Ischaemia Trial; Marker of Success (CHRISTMAS) Study randomised patients with ischaemic cardiomyopathy to carvedilol or placebo. Randomisation was stratified according to the presence or absence of hibernating myocardium at baseline. 2-dimensional and Doppler echo was performed at baseline by the randomising centres and analysed at a core laboratory. The Tei index is a Doppler derived index of myocardial performance that reflects both systolic and diastolic dysfunction and may therefore improve on standard echocardiographic predictors of outcome.

Methods: We analysed baseline echocardiographic data on the 387 patients to determine predictors of death or worsening heart failure over a 3 month follow up period. Variables included were the Tei index, LV wall motion index, mitral E and A wave velocities, E:A ratio, E wave deceleration time, isovolumic relaxation time (IVRT), aortic ejection time, baseline hibernation status, age, sex and treatment allocation.

Results: Stepwise logistic regression identified age, IVRT and the Tei index as independent predictors. Odds ratios were age (per year) 1.08 (95% CI 1.02-1.15), IVRT (per ms) 0.96 (0.94-0.98), Tei (per unit) 8.09 (1.54-42.41). The area under the ROC curve for this model was 0.776 (0.684-0.867). However both the Tei index and IVRT could be analysed by the core lab in only 149 (aged 63±8 years, 87% male, LV ejection fraction 29±10%) of the 387 patients.

Conclusion: In multicentre studies variables that are strongest predictors of outcome may be not be applicable to all patients. A balance has to be reached between variables that are recordable in all patients and those providing the strongest prognostic information.

P3533 How flow contraction, pressure recovery, and viscous resistance affect Doppler measurements across tunnel obstructions – An in-vitro study

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Background: We have previously shown that Doppler (D) measurements may not only underestimate pressure gradients across tunnel obstructions as reported by others but may also markedly overestimate them. This phenomenon was observed in tunnels as short as 5 mm and in settings where relevant pressure recovery distal to the obstruction was excluded. We suspected that the Doppler-catheter gradient relation in tunnel obstructions is determined by the combination of flow contraction, pressure recovery and viscous losses, which varies with diameter, length, inlet and outlet geometry of the tunnel.

Methods: To test this hypothesis, tunnels with a length of 20 mm, diameter of 5.5 mm and with gradually tapering inlet and/or outlet (20°) or with abrupt narrowing and/or expansion were studied in a pulsatile flow model. D and catheter (C) measurements were simultaneously performed. C gradients were estimated with the distal pressure port either at the tunnel entrance (dp C1), at the tunnel exit (dp C2) or 10 cm downstream (dp C3). Flow was visualized with a Laser system and recorded with a high-speed video camera.

Results: dp Do showed excellent agreement with dp C1 in all settings (mean difference 0.8±2.4 mmHg). In tunnels with abrupt narrowing, dp Do overestimated dp C2 by 54±19%. Flow visualization demonstrated that this dramatic change in lateral pressure within the tunnel was caused by marked flow contraction at the tunnel entrance resulting in a high velocity and low pressure field followed by readaption of the flow to the full cross-section with only little turbulence resulting in significant pressure recovery within the tunnel itself.

In contrast, in tunnels with gradually tapering inlet, dp Do underestimated dp C2 by 8±2%. In this setting, flow contraction was totally avoided and the neglection of viscous resistance in the simplified Bernoulli equation caused this D - C gradient discrepancy. Due to various extent of distal pressure recovery, dp C3 was 30±7% lower than dp C2 in tunnels with gradually tapering outlet but only 9 ±1% lower in abruptly expanding tunnels. This added various degrees of overestimation of dp C3 by dp Do.

Conclusion: Thus, the D - C gradient relation in tunnel obstructions is determined by the individual extent of (1) flow contraction with pressure recovery within the tunnel, (2) viscous resistance, and (3) pressure recovery distal to the tunnel. The predominance of one of these phenomena depends on inlet and outlet geometry, length and diameter of the obstruction. Overestimation and underestimation by Doppler as well as "pseudoagreement" can occur.

P3534 Transcutaneous continuous wave Doppler cardiac output monitoring of transpulmonary and transaortic flow is feasible

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Introduction: Monitoring cardiac output (CO) is important, particularly during anaesthesia, and in the acute care and coronary care for both adults and children, where early detection of changes in cardiac function allows planned therapeutic intervention. Continuous wave Doppler (CW) interrogation of intracardiac haemodynamics is an accurate, reproducible and noninvasive method of quantitating CO. Transcutaneous CW CO monitoring would be a useful application of quantitative echo.

Objectives: Determine the feasibility and reliability of transpulmonary (PV) and transaortic (AV) CW Doppler signal acquisition in supine free breathing subjects, and determine intra and inter observer variability of digital CO signal measurement.

Method: Digital PV and AV flow data were acquired using non-image guided CW Doppler (uscom) from 40 supine free breathing subjects (normal adults (n=10, age =20.3±2.5yrs, BSA=1.81±0.17m^2), normal children (n=10, age =9.9±1.8yrs, BSA=1.21±0.19 m^2), and 20 consecutive patients with cardiopulmonary disease) and compared with signals acquired in the left lateral decubitus position (con). 688 stroke cycles were analysed and haemodynamic parameters measured for each subject, each method and each valve. Reliability was tested by comparison of methods, and reproducibility tested by comparison of repeated and independent observations by a second inexpert observer.

Results: Signal acquisition from supine free breathing subjects was feasible in all cases with excellent correlation between all uscom and con heamodynamic parameters from both PV and AV flow, and repeated observations by the same and independent observers ($p<0.001$) with excellent regression and Bland-Altman statistics. Results from the inexpert and expert readers were not significantly different.

Normal uscom haemodynamic values

	Vpk (m/s)	Pmn (mmHg)	vti (cm)	vti x HR (m/min)
AV adults	1.27±0.14	3.51±0.79	25.1±3.1	18.1±2.9
PV adults	1.07±0.16	2.61±0.64	22.9±3.1	17.1±3.3
AV child	1.13±0.10	2.83±1.55	21.6±2.7	18.7±2.1
PV child	0.91±0.08	1.88±0.32	18.7±2.1	15.3±1.9

Conclusion: A transcutaneous CW ultrasound device that can deliver an accurate beat to beat CO signal may have multiple applications in the delivery of safe, improved and cost effective medical care.

P3535 Doppler echocardiographic assessment of pulmonary hypertension in mild-to-moderate chronic heart failure: prevalence and prognostic implications

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Pulmonary artery hypertension (PAH) is a frequent finding in patients with mild-to-moderate chronic heart failure, but it is not always easy to assess by Doppler echocardiography because of trivial flow velocity signals of tricuspid regurgitation.
This Doppler-echocardiographic study was carried out to evaluate prevalence and prognostic implications of PAH in patients with mild-to-moderate chronic heart failure and left ventricular (LV) dysfunction.
Two-hundred and fourteen patients with LV dysfunction (ejection fraction <45%) in NYHA class I-IV and sinus rhythm consecutively underwent a complete Doppler echocardiographic study. In case of weak or poor Doppler signals, PASP was measured after intravenous administration of a transpulmonary contrast agent (2.5 grams of Levovist at 400 mg/ml) or physiological saline. Patients were classified into three groups according to the degree of pulmonary artery systolic pressure (PASP): PASP <35 mmHg (absence of PAH), PASP between 35 and 50 mmHg (mild-to-moderate PAH) and PASP >50 mmHg (severe PAH). All patients were subsequently followed-up for a mean period of 22±14 months.
Overall, PASP was 45±14 mmHg and LV ejection fraction was 32±8%. Sixty-four percent of patients were in NYHA class I and II. In 27% of patients, PASP was estimated by the use of contrast. Prevalence of PAH was 67% (65 mild-to-moderate, 78 severe). During follow-up, 45 patients died from cardiac causes (17 sudden death, 28 progressive heart failure) and 38 were hospitalized for worsening heart failure. In the total study population, age >70 years, heart rate >80 beats per minute, PASP >35 mmHg were all independently associated with the combined end-point at multivariate Cox model. Probabilities of survival free from cardiac events were 74% in patients without PAH, 58% in those with mild-to-moderate PAH and 39% in those with severe PAH (p=0.001 by Log-rank). In patients with severe PAH, multivariate Cox analysis showed that only age (hazard ratio [HR]: 3.0, p=0.0037), restrictive mitral flow (HR: 2.7, p=0.0015) and more than mild mitral regurgitation (HR: 2.0, p=0.0033) were independent predictors of event-free survival.
By the use of echo-contrast agents, it was possible to determine noninvasively either prevalence or the prognostic impact of PAH in patients with mild-to-moderate chronic heart failure and LV dysfunction. Older age, restrictive filling and the degree of mitral regurgitation were all independently associated with the outcome of those with severe PAH.

P3536 Accurate measurement of the right atrial pressure using a simple direct noninvasive echocardiographic method: preliminary findings

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In last decade several attempts have been made to noninvasively estimate right atrial pressure (RAP) by two dimensional (2-D) and doppler echocardiography (echo); however, a noninvasive direct measurement of the RAP has been never proposed. Using a right supraclavicular approach in most of adult patients (pts),examined in the right lateral decubitus, it is possible to record a nearly 12-14 cm longitudinal straight conduit, formed by the right internal jugular vein, right innominate vein and superior vena cava, that, at the bottom, is intersected by the right pulmonary veins. Color flow imaging allows real time visualization of flows, i.e. blue coloured descending laminar flows, alternated with red-painted upward flows, coincident with the v and a waves of the jugular venous pulse. The distance between a zero reference point (zero reference pressure) and the apex of the ascending red flow, could be a direct measure of the RAP. The aim of this study was to assess feasibility, accuracy and limitations of this novel method of RAP estimation, comparing noninvasive (echo) vs hemodynamic (hemo) measurements blindly performed by two distinct operators. Methods 10 consecutive pts (6 men, age 61± 11), in which invasive RAP monitoring was carry out for acute ischemic syndromes, underwent 2-D and M-mode color doppler echo. Zero reference pressure was estimated at the midaxillary line for hemoRAP estimation. EchoRAP was measured, using 2-D and M-mode color doppler echo, from the inferior wall of the superior right pulmonary vein (zero reference pressure) to the apex of the red coloured upward flows caused by the systolic "v" or pre-systolic "a" waves of the jugular venous pulse. EchoRAP and hemoRAP measurements were converted from "cm of blood" and "cm of water" (H2O) into "mmHg", multiplying the values respectively by 0.78 and 0.74. Results: in all pts except for one, who presented an enlarged ascending aorta, superior vena cava was easily imaged. In 7 pts, who presented hemoRAP between 3.5 and 15 cm H2O (i.e. 2.5 and 11 mmHg), a good correlation was observed between non-invasive vs hemodynamic measurements of the RAP (4,69 ±2.66 vs 5.07± 2.64 mmHg, R=0.98). In one subject in which the hemoRAP was more than 20 cm H2O and in one with a negative hemoRAP (mean RAP= -2 cm H2O), no reliable value of the RAP was measured. Conclusion: within a RAP range between 2.5 and 11 mmHg, it appears possible to obtain an accurate noninvasive direct measurement of the RAP using 2-D and M-mode color doppler echo.

CARDIAC METABOLISM

P3537 Improvement in myocardial glucose uptake after five months of exercise training in patients with dilated cardiomyopathy

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The effect of exercise training on myocardial glucose uptake was studied in 15 clinically stable patients with dilated cardiomyopathy (NYHA class I-II) using positron emission tomography (PET) techniques. Eight of these patients (ejection fraction = 33±9%) participated in a 5 month endurance and strength training program at an intensity of 70% of peak oxygen consumption (VO2), while 7 patients (ejection fraction = 35±7%) served as non-trained control subjects. All patients remained on the same standard medical therapy including ACE inhibitors and β-blockers for the duration of the study. Measurements of left ventricular function were assessed using two-dimensional echocardiography. Myocardial glucose uptake was measured under euglycemic hyperinsulinemic clamp conditions using [18F]FDG and positron emission tomography (PET). The patients that participated in the training program exhibited a 16% increase in ejection fraction (33±9 to 38±9%; p=0.004) while no change was observed in the control group (35±7 to 37±6%; p=NS). Exercise training was also associated with a 27% increase in peak VO2 in the training group (19.9±4.2 to 25.2±5.2 ml/kg/min; p<0.001) while no change was noted in the control group (20.6±4.2 to 21.2±2.9 ml/kg/min; p=NS). There was no statistical difference in serum free fatty acid, serum insulin, and plasma glucose levels between either patient group. Baseline myocardial glucose uptake rates were improved in the training group from 39.6±18.7 to 48.1±18.5 μmol/100g/min (P=0.01) while no change was observed in the control group (from 49.9±18.4 to 48.0±19.0 μmol/100g/min). Myocardial glucose uptake calculated for the whole left ventricle also was significantly improved in the training group (162.6±92.9 to 194.6±99.9 μmol/min; p=0.04) compared to the control group (161.9±65.1 to 159.8±57.0 μmol/min; p=0.90). These results indicate that exercise training in this patient population improves myocardial glucose uptake. This improvement in glucose uptake may be indicative of a switch in myocardial preference to a more energy-efficient substrate.

P3538 Myocardial fatty acid oxidation is increased in patients with insulin dependent diabetes mellitus

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Objectives: In patients with insulin-dependent diabetes (IDDM) there is a decline in myocardial glucose utilization (MGU) that is paralleled by an increase in myocardial fatty acid utilization (MFAU) and oxidation (MFAO). It is unknown if the increase in MFAO simply reflects the increase in fatty acid uptake by the heart or an increase in the percent of extracted fatty acids that are oxidized. **Methods:** In 11 IDDM (3M; 36±11 yrs; HgbA1C 8.4±1.9%) and 5 normal volunteers (NV; 5M; 25±5 yrs) measurements of myocardial blood flow (MBF in mL/g/min), myocardial oxygen consumption (MVO2), MGU, MFAU and MFAO (all in umol/g/min) were measured by PET using O-15 water, C-11 acetate, C-11 glucose and C-11 palmitate respectively under resting conditions. The IDDM were studied during a low dose glucose-insulin infusion and NV were studied after a standard carbohydrate meal. All subjects were nonsmokers and were without hypertension and hyperlipidemia and had a normal rest/stress echocardiogram. **Results:** Plasma glucose, insulin, and lactate levels were comparable between the two groups (p=NS). However, plasma fatty acid levels were significantly higher in IDDM (0.59±0.25 umol/mL) compared to NV (0.15±0.06 umol/mL, P<.03). The rate pressure product was higher in IDDM compared with NV (p<.05). As a consequence, MBF and MVO2 tended to be higher when compared with NV (p=0.11 and 0.08, respectively). As expected, MGU was significantly lower in IDDM (0.21±0.11) compared with NV (0.46±0.21, p<.01). Both MFAU and MFAO were significantly higher in IDDM (0.21±0.14 and 0.21±0.13) compared with NV (0.03±0.02 and 0.02±0.02, p<.03 for both measurements). In addition, MFAO/MFAU in IDDM was increased when compared with NV (0.94±0.07 vs 0.83±0.14,p<.05). There was a negative correlation between MFAO/MFAU and plasma fatty acid levels in NV (r=-.93, p<.03) where there was no correlation in IDDM.
Conclusion: In IDDM, the percent of extracted fatty acid that is oxidized is increased. This increase cannot be explained solely by an elevation in plasma fatty acid levels. The increase in MFAO may help partially explain the increase in cardiac complications associated with IDDM.

P3539 Cardiac phantom measurement validating the methodology for a cardiac multi-center trial with positron emission tomography

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In an ongoing international multi-center trial, positron emission tomography (PET) is used to evaluate the effect of a new P-selectin antagonist on the infarct size in patients with acute myocardial infarction treated with thrombolysis. Although it is possible to correct for site-dependent factors, it is desirable to reduce these factors to a minimum. Therefore, an acquisition and reconstruction protocol have been defined that could be closely followed by all participating centers. The resulting reconstructed images are transferred to the core center for central processing with semi-automatic software. This paper reports on the multi-center phantom experiment that was carried out to assess the inter-center reproducibility of infarct size determination with this protocol. Also the spatial resolution of the short axis slices was examined. In addition, the analysis procedure was applied to normal PET-studies to evaluate the specificity of perfusion defect detection.

The transmural infarction in the phantom occupied 14.8% of the left ventricular area. The automated analysis was applied to the phantom measurements from the fourteen participating PET cameras. It yielded an accurate estimate of 15.1% with a standard deviation of 0.6%, indicating excellent reproducibility. The spatial resolution in the short axis slices was similar for all PET systems: 9.6 mm ± 0.8 mm. The same procedure produced an infarct size of zero in the studies of the normal volunteers.

The same phantom experiment was repeated on 14 scanners in 13 PET centers. Excellent inter-center reproducibility of defect size and global spatial resolution was observed, indicating that myocardial images from different PET-centers can be pooled for statistical analysis.

P3540 Myocardial perfusion and metabolic changes induced by biventricular pacing in patients with dilated myocardiopathy and conventional pacing

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Background: Biventricular pacing recently demonstrated to be useful in improving symptoms of medical refractory heart failure in patients (pts) with dilated myocardiopathy (DMC) and left bundle branch block (BBB) with a prolonged QRS duration. Preliminary experience with cardiac Positron Emission Tomography (PET) suggested that biventricular pacing could eliminate the interference on the myocardial metabolism of the septum induced by left BBB. Pts with chronic right ventricular apical pacing show enlarged QRS with a left BBB-like activation. Aim of this preliminary study was to verify if upgrading to biventricular pacing could ameliorate the metabolism of the septum in patients with DMC and chronic right ventricular pacing too.

Methods: We performed an upgrading to biventricular pacing in 3 male pts (mean age 73.7±4.7 years) with DMC and end stage heart failure (NYHA class III-IV) despite optimal medical therapy in whom a conventional right ventricular pacing system (DDD in 2 and VVIR in 1) had been implanted 74±71 months before. A third degree AV block without spontaneous rhythm faster than 40 bpm was present in 2 pts, while a second degree AV block with a right BBB morphology (QRS duration < 120 ms) was present in 1 pt. Permanent atrial fibrillation was present in 1 pt.

PET and echocardiogram were performed few days before and 3 months after the upgrading. Metabolism was evaluated using F18-fluorodeoxyglucose, by the glucose load-insulin technique, and perfusion by N13-ammonia, injected at rest. A visual and a semi quantitative analysis were performed. Left ventricular ejection fraction was determined by calculating the end-diastolic and end-systolic volumes according to Folland.

Results: During conventional right apical pacing all pts presented at the visual analysis of the PET a relatively reduced FDG uptake in the septum when compared to the NH3 uptake (0.670±0,130 vs 0.983±0.040, p=0.01). This reverse mismatch disappeared after upgrading to biventricular pacing (1.116±0.300 FDG uptake vs 0,997±0,244 NH3 uptake, p=0.08). Left ventricular ejection fraction remained unchanged after upgrading to biventricular pacing (19.3±6.0 vs 26.0±6.1, p=0.15)

Conclusion: These preliminary results suggest that: 1) in pts affected by DMC conventional right ventricular pacing induces an alteration in the metabolism of the septum similar to that observed in pts with left BBB and DCM; 2) upgrading to biventricular stimulation eliminates this reverse mismatch.

P3541 Early determination of oxidative metabolism and development of perfusion and myocardial damage in acute ST-segment elevation myocardial infarction

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Patients with acute ST-elevation myocardial infarction who obtain early reperfusion with TIMI grade 3 flow in the infarct related artery will have the best prognosis. It has been reported that oxidative metabolism after successful reperfusion was a stronger predictor than perfusion regarding left ventricular recovery.

Methods: In eight patients PET was performed as early as 3 h after start of fibrinolysis. The myocardium was divided into four regions, remote, border remote, border infarct and infarct region. The oxidative metabolism was determined with 1-11C-acetate, MBF (myocardial blood flow) and PTF (fraction (g/ml) of myocardial tissue capable of rapidly exchanging 15O-water) with 15O-water. PET investigations were also performed after 24 h and after 3 weeks (MBF and PTF).

Results: The myocardial perfusion and oxidative metabolism decreased closer to the infarct region. PTF (related to remote) was low at 3 h in the infarct and in the border infarct region and was significantly increasing over time (p=0.02 and p=0.01). Relative myocardial perfusion did not show any significant changes over time and there was no consistent correlation to PTF. However, oxidative metabolism at 3 h was correlated to PTF in the infarct area at 3 and 24 h and after 3 weeks (p= <0.01, r=0.96; p=0.04, r=0.79 and p=0.052, r=0.75.

Conclusions: Oxidative metabolism, determined as soon as 3 hours after start of fibrinolysis, correlated to PTF over time in the infarct area which myocardial perfusion did not. Further, PTF increased significantly over time. This suggests that further development of reperfusion treatment is needed, to achieve earlier and more complete restoration of myocardial perfusion and oxidative metabolism and PET might be useful in assessing treatment efficacy.

P3542 Influence of myocardial energetics on exercise capacity in patients with dilated cardilmyopathy

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Twenty clinically stable patients with dilated cardiomyopathy (DCM) and 13 apparently healthy age-matched controls were studied in order to determine the extent that myocardial perfusion and energetics effect peak exercise capacity (VO2). All study subjects underwent a symptom limited, incremental cycle ergometer test with respiratory gas analysis to volitional fatigue. Myocardial perfusion and biventricular oxidative metabolism were measured using positron emission tomography (PET) techniques along with [15O]H2O and the monoexponential clearance rate of [11C]acetate (kmono), respectively. Hyperemic perfusion was measured after dipyridamole (0.56 mg/kg per min) administration. Perfusion reserve was calculated as the ratio of hyperemic to resting perfusion. The ratio between right and left ventricular oxidative metabolism (Kratio) was also calculated. Basal myocardial perfusion (0.86 ± 0.17 vs. 1.00 ± 0.21 ml/min/g; p = 0.04), hyperemic perfusion (1.73±0.83 vs. 3.01±1.20 ml/min/g; p<0.001), and perfusion reserve (2.01±0.91 vs. 3.08 ±1.35 ml/min/g; p=0.01) were all lower in the DCM patients compared to the healthy subjects, respectively. There was no difference in left ventricular oxidative metabolism (LVkmono) between the two groups (0.066 ± 0.015 vs. 0.070 ± 0.012 per min; p = 0.40), however, the DCM patients had a significantly higher right ventricle kmono level (0.051 ± 0.007 per min) compared to the healthy subjects (0.043 ± 0.009 per min; p=0.007). Consequently, the Kratio was also higher in the DCM patients (0.81±0.17) compared to the healthy subjects (0.62±0.09; P=0.001). When assessing the relationship between exercise capacity and various myocardial parameters in the DCM patients, the strongest correlation was found between Kratio and exercise capacity (r=-.68, P=0.001). A positive correlation was also found between exercise capacity and myocardial perfusion reserve (r=0.62, p=0.004). Regression analysis showed that the combination of these two parameters explained 47% of the variability in peak exercise capacity. When further analyzing the relationship between exercise capacity and myocardial energetics, patients with a Kratio greater than the lowest value obtained from the healthy subjects (0.8) had a significantly lower exercise capacity (16.2±2.8 ml/kg/min) compared to patients with a Kratio less than 0.8 (21.0±4.0 ml/kg/min; P<0.001). These findings indicate that exercise capacity is associated with myocardial energetics in patients with DCM and mild heart failure.

P3543 Myocardial blood flow and viability in patients with left ventricular dysfunction secondary to coronary disease

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The identification of viable myocardium in patients with chronic left ventricular (LV) dysfunction and coronary artery disease (CAD) is important to select patients who may benefit from revascularisation. The extent of hibernating myocardium may be predicted by myocardial glucose uptake (MGU) measured by positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG). The relationship between myocardial hibernation and myocardial blood flow (MBF) is the subject of continuing debate. Similarly, the prevalence of dysfunctional but viable myocardium in this increasingly common group of patients remains unclear. We therefore measured MBF and myocardial viability in patients with impaired LV function and CAD referred for bypass surgery (CABG).

Patients and Methods: 114 patients (aged 60.2 ± 8.8 yrs) with significant LV dysfunction (LV ejection fraction <35%, mean 26 ± 10%) and multivessel CAD were studied. MBF was measured using oxygen-15 labelled water at rest and during adenosine infusion (140 μg/kg/min). MGU determined by quantitative PET during hyperinsulinaemic clamp. A 16-segment LV model was used for PET data analysis.

Results: Global resting MBF in patients was similar to normal volunteers (0.84 ± 0.28 vs 0.90 ± 0.14 ml/min/g, P=NS) but markedly blunted during adenosine (1.27 ± 0.63 vs 3.57 ± 0.84 ml/min/g, P<0.001). In patients, overall MGU was 0.41 ± 0.21μmol/min/g and in 83% of LV segments MGU was >0.25 μmol/min/g (previously found to optimally predict viability). A stepwise decline in hyperaemic MBF, MGU and an increase in prevalence of non-viable segments was noted as MBF decreased (table).

Quartile MBF(ml/min/g)	>1.02	0.81 - 1.01	0.65 - 0.80	<0.64
No segments	371	374	374	370
MGU (micromol/min/g)	0.51 ± 0.22	0.43 ± 0.21	0.39 ± 0.18	0.35 ± 0.15
MBF (Adenosine)	1.50 ± 0.71	1.28 ± 0.56	1.25 ± 0.61	1.05 ± 0.56
% non viable	9	16	20	23

ANOVA: P<0.001 for each column vs Q1

Conclusions: Viable dysfunctional myocardium is common in patients with impaired LV function and CAD. The reduction in segmental MGU in association with lower resting and peak MBF suggests that the ability of the heart to withstand ischaemia and number of viable myocytes that will benefit from revascularisation also declines.

P3544 Cardiac power output and myocardial blood flow during dobutamine stress in patients with coronary artery disease

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Patients with coronary artery disease (CAD) treated medically are frequently limited by breathlessness rather than angina that is thought to be secondary to the limited ability of the heart to increase cardiac output in response to demand. To probe this further we used positron emission tomography to simultaneously assess cardiac power and myocardial blood flow in response to dobutamine stress in patients with CAD whose exercise tolerance was limited by breathlessness.

Subjects and Methods: Comparison was made between 9 male healthy volunteers (age 57±7 (mean±SD) yrs) and 11 patients (age 63±8 yrs) with CAD who were limited on exercise by breathlessness rather than angina pectoris. All subjects had normal resting left ventricular (LV) function at echocardiography and the patients had >50% stenosis in 2 or more major coronary arteries. Myocardial blood flow (MBF) and cardiac output (CO) were measured using the flow tracer oxygen 15-labelled water (10 MBq/Kg) at baseline and at peak dobutamine stress. Beta-blockers and calcium antagonists were withdrawn 72 hours prior to the study and other anti-anginal medication withdrawn on the day of the study. A single tissue compartment tracer kinetic model was used to calculate global MBF (ml/min/g) and CO. Cardiac power output was calculated as CO x MAP x K watts (where MAP is mean arterial pressure and K conversion factor 0.00222).

Results: Resting CO was 4.13 ± 1.27 l/min in volunteers and 4.21 ± 0.76 l/min in patients and MBF 0.81 ± 0.16 ml/min/g and 0.89 ± 0.22 ml/min/g respectively. The mean increase in cardiac output after dobutamine was 3.05 ± 1.1l/min in the volunteers and 2.3 ± 0.8 l/min in the patients (P<0.05). The corresponding changes in cardiac power output were 0.81 ± 0.31W and 0.66 ± 0.35W respectively (P<0.01). In the volunteers, the increase in MBF was 1.89 ± 0.72 ml/min/g but only 0.79 ± 0.37 ml/min/g in the patients (P<0.01). The relationship between rate-pressure product and MBF was maintained in both patients and volunteers, although peak cardiac power occurred at lower MBF in the patients consistent with demand ischaemia.

Conclusion: In patients with stable CAD and normal resting LV function, the increase in cardiac output and power in response to dobutamine is limited by the failure of MBF to rise appropriately although the relationship between MBF and RPP is maintained.

P3545 Impact of estrogen on myocardial fatty acid utilization and oxidation in postmenopausal women

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Objectives: Results of studies in experimental animals have demonstrated that estrogen enhances myocardial fatty acid utilization (MFAU) and oxidation (MFAO) primarily through its modulation of the perioxsome proliferator receptor alpha system. Whether estrogen plays a similar role in myocardial lipid homeostasis in humans is unknown.

Methods: Measurements of myocardial blood flow (MBF in mL/g/min) oxygen consumption (MVO2), glucose utilization (MGU), MFAU and MFAO (all in nmol/g/min)were measured by PET using O-15 water, C-11 acetate, C-11 glucose, and C-11 palmitate, respectively. Under resting conditions and in the fasted state, measurements were obtained in 10 older males (OM, 67 ± 6 yrs), 6 older females not taking estrogen (OF, 68 ± 5 yrs) and in 5 females on long-term estrogen therapy (OFE, 64 ± 2 yrs). All subjects were nonsmokers and were without hypertension and hyperlipidemia and had a normal rest-stress echocardiogram.

Results: Plasma glucose, insulin, and fatty acid levels were comparable between the three groups (p=NS). Plasma lactate levels tended to be higher in OM compared with OF or OFE (p < 0.07). The rate pressure product tended to be higher in the OM compared with the OFE (p=.16). As we have shown previously, MBF/RPP was higher in both OF (2.21±0.26 x 10,000 mmHg x BPM) and OFE (2.31±0.86 x 10,000 mmHg x BPM) compared with OM (1.65±0.38x10,000 mmHg x BPM, p<.001). MVO2/RPP was significantly higher in OFE (1.35±0.48 mmHgxBPM) compared with OM (0.81±0.25 mmHgxBPM, p<.03) or OF (1.03±0.33 mmHgxBPM, p<.03). MGU/RPP did not differ among the three groups. However, MFAU/RPP was highest in OFE (0.049±0.019 mmHgxBPM) than either OF (0.033±0.005 mmHgxBPM, p<.02) or OM (0.029±0.01 mmHgxBPM, p<.02). Similarly, MFAO/RPP was highest in OFE (0.047±0.018 mmHgxBPM) compared with either OF (0.029±0.005 mmHgxBPM, p<.007) or OM (0.025±0.001 mmHgxBPM, p<.007).

Conclusion: In healthy postmenopausal women, estrogen replacement therapy stimulates MFAU and MFAO which may also result in an increase in MVO2. Whether similar effects occur in men are unknown. The effect of estrogen on myocardial lipid homeostasis may help explain some of the conflicting observations regarding estrogen replacement therapy and cardiovascular risk in postmenopausal women.

P3546 Intramitochondrial beta-oxidative fatty acid metabolism accelerating in spite of preferably a little energy fuels in chronic heart failure

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Background: Fatty acid are used as a major fuel in the fed state of heart, and 123I-beta-methyl-iodophenylpentadecanoic acid (BMIPP) is available for assessing mitochondrial metabolic function, but the metabolism in heart failure remained to be not clarified. 9-methyl-pentadecanoic acid (9MPA) is converted to 3-methyl-nonanoic acid (3MNA) by beta-oxidation in mitochondrium and then to p-iodophenylacetic acid (PIPA) as the next metabolite through additional beta-oxidation after alpha-oxidation. We investigated fatty acid metabolism in chronic heart failure using BMIPP and 9-MPA.
Methods: Autoimmune myocarditis was induced in Lewis rats by injection of porcine cardiac myosin. Three groups were designed as normal control(NC group), chronic heart failure(CHF group; 60th day after injection), and therapy group(Tx group; chinapril, angiotensin converting enzyme inhibitor, 2mg/kg/day in chronic phase). Rats were injected BMIPP(0.7MBq) or 9-MPA(1.0MBq), and then sacrifised after 3 min., 10 min., 30 min. and 60 min. We examined hemodynamic parameters, pathological findings, and fatty acid metabolism. The myocardial uptakes of BMIPP and 9-MPA were examined as %dose/g tissue and differential absorption ratio (DAR) corrected with body weight. The metabolism were analyzed by NIH image quantitatively substrate pattern of 9-MPA, 3-MNA, and PIPA fraction on thin layer chromatography(TLC).
Results: Left ventricular weight/body weight ratio was increased in CHF group(0.440%) compared with NC group(0.260%)($p<0.0001$), and it was reduced in Tx group(0.328%)($p<0.0001$). Histological changes such as fibrosis were prominent in CHF compared with control and Tx group. The myocardial uptakes of BMIPP and 9MPA were reduced in CHF compared with NC(1.617% vs 2.097%, $p<0.05$). According to quantitative analysis of metabolite fraction, in CHF 3MNA ratio(11.4% vs 6.6%) at 3 min., PIPA ratio(8.7% vs 6.3%) and 3MNA and PIPA ratio(15.7% vs 11.1%) at 10 min. were increased compared with NC(respectively $p<0.05$), and then also this ratio tendency remained until 60 min($p<0.01$), instead of TG pool amounts was not different among all. Therapy made intermittent metabolites(3MNA and PIPA) ratio at 10 min. and 60 min. decreased compared with CHF(respectively $p<0.05$ and $p<0.01$)
Conclusions: In chronic heart failure, the uptake of fatty acid were decreased and fatty acid metabolism was suppressed, but our deta suggested intramitochondrial beta oxidative metabolism were accelerated in spite of preferably a little energy fuels.

P3547 Myocardial fatty acid imaging and expression of peroxisome proliferator-activated receptor in volume-overloaded rabbit hearts

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The peroxisome proliferator-activated receptor (PPAR)-alpha is a member of the nuclear receptor superfamily and regulates gene expression of fatty acid utilization enzymes. In cardiac hypertrophy and heart failure by pressure-overload, myocardial energy utilization reverts to the fetal pattern, and metabolic substrate switches from fatty acid to glucose. However, myocardial metabolism in volume-overloaded hearts has not been rigorously studied. The aim of the present study was to examine fatty acid metabolism and PPAR-alpha expression in volume-overloaded rabbit hearts. Volume-overload was induced by carotid-jugular shunt formation. Sham operated rabbits were used as control. Chronic volume-overload increased left ventricular weight (4.1 ± 0.2 g vs. 6.1 ± 0.5 g, $P < 0.01$) and ventricular cavity size (12.8 ± 0.5 mm vs. 17.5 ± 0.5 mm, $P < 0.01$), and relative wall thickness was decreased (0.40 ± 0.02 vs. 0.28 ± 0.01, $P < 0.01$), indicating eccentric cardiac hypertrophy. Iodine-125-iodophenyl 9-methylpentadecanoic acid (9MPA) was intravenously administered, and animals were sacrificed at 5 min after tracer injection. The 9MPA was rapidly metabolized to iodophenyl-3-methylnonanoic acid (3MNA) by beta-oxidation. Lipid extraction from the myocardium was performed by the Folch method, and the radioactivity distribution of metabolites was assayed by thin-layer chromatography. Total RNA was extracted from the myocardium, and levels of PPAR-alpha mRNA were examined by semi-quantitative reverse transcriptase polymerase chain reaction (RT-PCR). Myocardial distribution of 9MPA was more heterogeneous in shunt than in sham rabbits ($P < 0.05$). In volume-overloaded hearts by shunt, the conversion from 9MPA to 3MNA was faster than in sham control hearts (56 ± 18 vs. 39 ± 3%dose/mg tissue, $P < 0.05$). However, mRNA expression of PPAR-alpha was downregulated in shunt rabbits compared to sham rabbits ($P < 0.05$). These data suggest that myocardial fatty acid metabolism was altered in eccentric cardiac hypertrophy by volume-overload.

CORONARY ANGIOGRAPHY

P3548 Coronary artery stenosis can be predicted by the presence of typical angina symptoms

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An appropriately taken history is the richest source of information concerning ischaemic heart disease. The study goal was to determine the predictive value of angina-like symptoms in the diagnosis of stenotic changes within coronary arteries. A prospective study was performed in 250 patients (26 - 75 years old, 187 male, 64 female) who had coronary angiography due to their angina symptoms. No patient had known previous myocardial infarction. According to their symptoms all patients were divided into typical or atypical angina group. The typical angina was defined as the presence of a pain in typical (retrosternal) location, triggered by exercise or stress and relieved by sublingual nitrates or rest. Any kind of angina that could not fulfil these criteria was characterised as an atypical one. We evaluated specificity, sensitivity, and positive and negative predictive value of angina-like symptoms according to the results of coronary angiography (narrowing of artery lumen $\geq$ 50% in at least 1 vessel). Additionally, an unadjusted and adjusted for age, sex, history of smoking, hypertension and diabetes mellitus logistic regression analysis was performed for prediction of the presence of any significant stenotic change in coronary arteries. Logistic regression results are presented as an odds ratio with 95% confidence interval (CI). The presence of typical angina was associated with specificity of 79.55%, sensitivity of 84.66%, positive predictive value of 88.46% and negative predictive value of 73.68%. Odds ratio for typical angina symptoms and the presence of coronary stenosis in the unadjusted logistic regression was 21.47 (95% CI: 10.98 - 41.98; $p < 0.0001$) whereas in the adjusted analysis it was 23.13 (95% CI: 10.59 - 50.53; $p < 0.0001$). The obtained results indicate that typical angina symptoms have a high predictive value for the presence of significant stenosis within coronary arteries. It confirms also that a carefully taken patient history is still a powerful diagnostic tool in coronary artery disease.

P3549 Comparison of TIMI frame counts of patients with and without coronary artery ectasia

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Background: Thromblysis In Myocardial Infarction (TIMI) frame count is a simple clinical tool for assessing quantitative indexes of coronary blood flow. Coronary artery ectasia,(CAE) is characterized by segmental or diffuse dilatation of the coronary arteries to >1.5 the diameter of the adjacent segments of the same artery or of different artery. In this study we aimed to evaluate the coronary flow in patients with CAE by the means of TIMI frame count (TFC) and to compare with subjects who have angiographycally normal coronary arteries.
Materials and Methods: Study population consisted of 37 patients with coronary artery ectasia only in the right coronary artery (RCA). To be included in the study, patients also needed to have no significant stenostic lesion (>50%) in the coronary three, no valvular heart disease, previous myocardial infarction, and no wall motion abnormalities with echocardiography. Control group consisted of 31 patients with angiographically proven normal coronary arteries.
Results: There are no statistically significant differences between two groups in respect to age, gender, presence of hypertension, smoking ($p>0.05$ for all). TIMI frame count of RCA in the study group was significantly higher than in that of control group(51 ± 17 vs 25 ± 8 $p<0.001$ respectively). TIMI frame counts of the study group for left anterior descending (LAD) and left circumfle(LCx) coronary artery were also significantly higher than those of control group (Corrected TFC for LAD=42 ± 11 vs 24 ± 7 respectively $p<0.001$, TFC for LCx; 44 ± 15 vs 25 ± 9 respectively $p<0.001$). In patients with CAE, TFC of the RCA was higher than that of LAD and LCx coronary artery(51 ± 17 vs 42 ± 11 and 44 ± 15 respectively $p<0.05$). TIMI frame count of the RCA showed significant correlation with the TFC of the LAD($r=0.422$ $p<0.01$) and LCx coronary arteries($r=0.530$, $p<0.01$).
Conclusion: Patients with CAE have significantly increased TFC when compared to patients with normal coronary arteries. In one vessel ectasic patients, TFC of non-ectasic vessels is also significantly higher than that of patients with normal coronary arteries. Significant correlation between the TFCs of ectasic and non-ectasic vessels in the same patients has also suggested that the mechanism underlying CAE, affects the coronary flow even in non-ectasic vessels.

P3550 Comparison of clinical state and quality of life of patients with and without angiographic follow-up after coronary angioplasty

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Background: Angiographic follow-up is normally scheduled 6 months after percutaneous transluminal coronary angioplasty (PTCA) and stent implantation (SI). The common experience is, that 10-20% of the patients do not appear for follow-up. It would be important to know whether the drop-out might be informative to take this into account when planning clinical trials, and interpreting their results.
Methods: We included 49 patients with single-vessel coronary artery disease treated by PTCA and SI who did never appear for follow-up. The examination was done 2-18 months after the scheduled follow-up date and consisted of recording the CCS class, answering a questionnaire regarding satisfaction with health (SH), physical functioning (PF), heart-related discomfort (HD) and physical exhaustion (PE), and performing a structured interview on physical activity, comorbidity and use of medication. This cohort was compared to a sample of 104 patients who visited the hospital for angiographic follow-up, and underwent the same examination besides the routine clinical procedures.
Results: Patients without follow-up were more likely to be free of symptoms of angina (OR=3.1 to have CCS-0, 95% C.I.: [1.5,6.5]) and reported less HD (4.1 vs 5.4 points on a 24 point scale, 95% C.I. for difference of means [0.0,2.8]). The two groups were not distinguishable in SH, PF and PE. A non-significant but remarkable difference was noticed among patients with CCS-0: Nitrate was more often used by patients without follow-up (21% vs 8%, P=0.17). Nonetheless, the clinical difference between the cohorts is still significant when adjusting for nitrate (OR=2.0 for CCS-0 and no use of nitrate, 95% C.I. [1.0,4.0]). Among patients without follow-up who were classified as CCS-0, those ones using nitrate reported more HD (P=0.06) and PE (P<0.001), and less PF (P=0.004) and SH (P=0.1) in comparison to patients not using nitrate.
Conclusions: Drop-outs by missing the angiographic follow-up should be considered to be informative. When evaluating only patients seen at the follow-up examination, the mean clinical success of the treatment is underestimated. In randomized clinical trials, differences between treatments measured by endpoints related to symptoms of angina may be underestimated. In addition, patients who prefer to avoid follow-up angiography should be encouraged to undergo the non-invasive clinical examinations. Physicians should consider the possibility that apparently angina-free patients might suppress serious symptoms by the use of nitrate.

P3551 High incidence of microcirculation abnormality produced by percutaneus transluminal coronary rotational athrectomy (PTCRA)

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Background: Potential risk of microcirculation abnormality produced by embolization of abraded non-compliant plaque, platelet aggregation, and vasospasm is an important issue. However, the incidence of perfusion and functional abnormality caused by PTCRA is not fully known yet.
Methods: Serial 99mTc-tetrofosmin QGS SPECT were performed before and just after coronary intervention in 39 patients (21: Rotablator, 18: POBA and Stenting) to assess the acute effect to myocardial perfusion and function.
Results: Procedural success with TIMI 3 flow was aschieved in all patients. Patients with PTCRA experienced significantly high incidence of ST segment elevation(4 out of 21 patients) and scintigraphical deterioration in perfusion (14 of 21 patients) compared with POBA and stenting, although no significant difference of functional deterioration was observed.

Change of QGS parameter after PCI

	PTCRA	Other devices	p value
prolonged ST elevation	4/21	0/18	n.s
perfusion abnormality	14/21	3/18	0.005
change of extent score	14.8 (SD 16.2)	-3.0 (21.7)	0.005
change of severity score	30.4 (SD 32.9)	-7.6 (SD 39.6)	0.002
change of EDV	-6.0 (SD 15.8)	-4.8 (SD 12.4)	n.s
change of ESV	0.1 (SD 8.1)	1.4 (SD 8.9)	n.s
change of LVEF	-1.0 (SD 24.2)	-3.4 (SD 5.0)	n.s

Conclusion: Patients treated with PTCRA were more likely to experience microcirculation abnormality compared with POBA and stenting. And alteration of perfusion is more sensitive to detect the microcirculation abnormality than ECG and functional parameters.

P3552 Relation between coronary and renal atherosclerosis in hypertensive patients referred for coronary angiography

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Aim: To search for prevalence of renal atherosclerotic involvement in hypertensive patients referred for coronary angiography and investigate the relation between the coronary and renal atherosclerotic involvement. **Method:** We performed selective renal angiography after coronary angiography in hypertensive patients who were referred for a coronary angiogram. Demographic variables, coronary artery disease (CAD) risk factor profile and lipid profiles of the patients were collected. So as to score the severity of coronary atherosclerosis we used the "Gensini" scoring system. In order to score the severity of the atherosclerotic involvement in renal arteries, we first visually graded per cent stenosis in each renal artery into quartiles and gave a score from 0 to 4, the cumulative for both renal arteries equaled to renal artery score for each patient. Patients who had a myocardial infarction in the preceding month were not included. **Results:** We performed selective renal angiograms to 148 hypertensive patients at the end of the coronary angiography. They were aged 37-78 (60.2 ± 9.5), and 92 of them (62.2%) were men. Thirty-eight patients (25.6%) of the study cohort had either completely normal coronary arteries or atheorsclerotic plaque of < 50%. We found varying degrees of renal atherosclerotic involvement in 27 patients (18.2%). We considered renal atherosclerotic involvement of equal to or more than 50% as significant. Excluding only one patient with a 40% renal artery stenosis, all out of the 27 had significant CAD. Eight out of 27 had lesions more than 50% (5.4%) and 3 of the 8 had renal interventions (2 renal stent implantation, 1 operation). In correlation analysis we found a mild degree of correlation between the Gensini and renal score and age and renal score ($r = 0.45$, $p<0.001$) and ($r = 0.32$, $p<0.001$) respectively. Multivariate logistic regression analysis revealed 2-3 vessel disease as an independent risk factor for significant renal atherosclerotic involvement (p=0.04, relative risk =6.4) **Conclusion:** Renal atherosclerotic involvement is quite common among hypertensive patients referred for coronary angiography (18.2%). Diffuse CAD might be a risk factor for renal atherosclerotic involvement. So as to exclude renovascular hypertension and detect and follow-up low grade renal atherosclerotic involvement, it seems prudent to perform renal angiography routinely to hypertensive patients referred for coronary angiography.

P3553 Increased WBC count independently predicts presence of multiple complex plaques in patients with history of unstable angina

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Background: Complex appearance of atherosclerotic lesion on angiography may reflect its instability. Subsequently, presence of multiple complex (MC) lesions has been shown to predict worse prognosis in patients with coronary artery disease (CAD). Inflammation has been demonstrated to be an important contributor for the development of vulnerable atherosclerotic plaque. A level of inflammation may be assessed by white blood cell (WBC) count. Therefore we sought to assess whether presence of multiple complex plaques seen in coronary arteries of patients with history of unstable angina may be related independently of classical risk factors to intensity of systemic inflammatory activation as measured by WBC count. **Methods:** We prospectively assessed 212 consecutive patients (148 males, age 60,2±10,3) with history of unstable angina within preceding 6 months, who underwent coronary angiography. Baseline characteristics and WBC count ($10^3/\mu l$) was assessed within 48hrs prior to cardiac catheterization. Coronary angiograms were analyzed and all plaques ≥30% stenosis were classified into complex or smooth groups. Complex plaque was defined if irregularities, ulcerations, total occlusion or thrombus were present and the remaining accounted smooth lesions. Multiple lesions were defined as ≥2 plaques. To reveal independent predictors of presence of MC plaques history of DM, hypertension, hyperlipidemia, family history, smoking, age, sex, BMI, WBC count and number of all identified coronary plaques were analysed using multivariate logistic regression. **Results:** Angiographically complex plaques number was 305 out of all 706 plaques identified on angiography. 83 patients who had MC plaques had higher WBC count than remaining patients (student's T-test; 8,0±2,4 vs 7,1±2,2 respectively, p=0,009.). Multivariate analysis revealed that the only independent predictors of presence of multiple complex (MC) plaques were WBC count (OR 1,19; 95%CI (1,02-1,39); p=0,023) and number of all plaques (OR 2,45; 95%CI (1,88-3,21); p<0,0001). **Conclusion:** Intensity of systemic inflammatory activation expressed by WBC count is linked independently to increased incidence of multiple complex lesions. Our findings suggest that enhanced inflammation may adversely influence prognosis not only by modification of plaque structure but also by increasing number of vulnerable atherosclerotic lesions.

P3554 Long-term clinical outcome of IVUS-guided versus angio-guided stenting. A meta-analysis of published studies

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Background: Intracoronary ultrasound (IVUS) has provided insights into the mechanism of percutaneous coronary interventions (PCI) as well as the pattern and mechanism of restenosis. Prior studies have demonstrated that the use of IVUS measurements of vascular dimensions improves angiographic results of PCI, mostly when a stent is deployed. To date only few underpowered studies (a mixture of small, randomized or observational trials) comparing the clinical efficacy of IVUS-guided versus Angio-guided stenting have been performed and odds ratios (OR) vary substantially between them. Thus, the present investigation refines these values by means of a formal meta-analysis.
Methods: Nine studies were considered suitable for analysis. Odd Ratios (OR) were calculated for 6-month clinical follow-up. Primary end points were a composite of death and non-fatal MI as well as binary restenosis, as considered in every single study. Secondary end points were a composite of death, reinfarction and target vessel revascularisation (MACE), according to single study definition, and individual cardiac events as well.
RISULTS. A total of 2972 patients were included. At 6 month, the OR for death and non-fatal MI was 1,13 (95% Confidence Interval [IC], 0,79-1,61, p=0,5) for patients with IVUS-guided vs. Angio-guided stenting. Patients treated with IVUS-guided stenting had significantly less restenosis (OR 0,75, 95% CI 0,60-0,94, p=0,01). In addition, patients treated with IVUS-guided stenting had less TVR (OR 0,62, 95% CI 0,49-0,78, p=0,00003) and MACE (OR 0,79, 95% CI 0,64-0,98, p=0,03) compared to Angio-guided stenting. Death (OR 1,0, 95% CI 0,42-2,38, p=NS) and non-fatal MI (OR 1,14, 95% CI 0,78-1,64, p=0,5) were similar between the two groups.
Conclusions: IVUS-guided stenting implantation does not confer any substantial advantage on long-term clinical outcomes compared to an angiographic-guided optimisation. However, IVUS-guided stenting significantly reduces 6-month angiographic restenosis and TVR. This additional benefit could be very helpful when treating lesions with high risk of restenosis like small vessel, long lesion or vein grafts.

P3555 Do spatial wall shear stress gradients affect left coronary atherosclerosis location?

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Introduction: Spatial Wall Shear Stress Gradient (SWSSG) in vitro has shown its importance in atherogenesis, probably as local modulator of endothelial gene expression. The purpose of our study is to numerically analyze the SWSSG distribution over the normal human Left Coronary Artery (LCA) tree.
Methods: A three-dimensional computer generated model of the LCA tree, based on averaged human data set extracted from angiographies and reported previously, was adopted for subsequent analysis. The LCA tree includes Left Anterior Descending (LAD), Left Circumflex Artery (LCxA) and their major branches. A steady, plug flow corresponding to resting conditions (0.17 m/s) was applied, whereas the blood was treated as non-Newtonian fluid. Discharges from distal branches were set proportional to the third power of the corresponding branch diameter. The governing Navier-Stokes flow equations were solved using a previously validated finite-element solver. The SWSSG is calculated using 40,843 grid nodes throughout the tree extension.
Results: Computational results indicate that on the left main coronary artery bifurcation the SWSSG ranges between 0.2 and 1.7 dyn/cm^3. In the LAD, minimum values of SWSSG are in the order of 0.3 dyn/cm^3, occurring around the origin of first diagonal branch, whereas maximum values are of the order 12.5 dyn/cm^3, occurring on the distal segment of the LAD at the apex, where high shear stress values, also, coexist. In the LCxA there is a predilection of low SWSSG (0.4 dyn/cm^3), occurring around the origin of the first marginal branch, whereas the highest values are of the order 5.2 dyn/cm^3 occurring at the distal segment of the second obtuse marginal. Again, high shear stress values coexist with high SWSSG. Spatial gradients of wall shear stress attain large values at small caliber branches. Furthermore, the general pattern of SWSSG distribution is in accordance to the wall shear stress distribution.
Conclusions: Low SWSSG occurs nearby to and at bifurcations, particularly at regions opposite to the flow divider, which are anatomic sites predisposed for atherosclerotic development. In general, low SWSSG appear in the proximal regions of the LCA tree, where atherosclerosis frequently occurs. At distal segments the SWSSG increases substantially due, perhaps, to increased velocity resulted from increased vessel tapering. Probably, wall shear stress gradients can be established as a reliable predictor for atherosclerosis location.

P3556 Wall shear stress differences between proximal and distal left coronary artery bifurcations

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Introduction: The coronary left artery, generally, demonstrates the most intense atherosclerosis involvement within its first few centimeters, exhibiting particular predilection to proximal bifurcation regions. The purpose of our study was to quantitatively analyze the three-dimensional (3D) wall shear stress differences between proximal and distal bifurcations of the human Left Coronary Artery (LCA) tree.
Methods: A 3D computer model of the normal LCA tree, reported previously, was adopted for numerical analysis. Uniform flow corresponding to resting conditions was applied at the LCA tree inlet. The governing mass, momentum and energy flow equations were solved using a previously validated numerical code. Wall shear stress was calculated at the following bifurcation regions: 1) left main coronary artery (LMCA), 2) first obtuse marginal (OM1), 3) second obtuse marginal branch (OM2), 4) first (D1S1), 5) second (D2S2), and 6) third (D3S3) diagonal and septal branches. The number of utilized grid nodes of the bifurcation regions was ranged between 6000-13000, depending upon the physical size of the lumen as well as the wall shear gradient.
Results: The computed average wall shear stress at the LMCA was found to be 3.93±0.01 N/m^2, at OM1 6.45±0.05 N/m^2, at OM2 7.24±0.03 N/m^2, at D1S1 6.30±0.01 N/m^2, at D2S2 7.21±0.01 N/m^2 and finally at D3S3 10.72±0.07 N/m^2, ($p<0.001$ for all above cases). Results indicate that wall shear stress increases gradually from proximal to distal bifurcations.
Conclusions: Low wall shear stress values occur at the proximal bifurcations of the LCA tree. Shear stress increases gradually from proximal to distal bifurcation regions. At the very distal segments this increment becomes substantial. Low wall shear stress bifurcation regions agree well with preferred sites of atherosclerotic coronary lesions in humans.

P3557 Sustained clinical benefit of IVUS guided stenting for long coronary artery stenoses: long-term follow-up of a randomized study

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Background: Long coronary lesions treated with stent implantation (SI) have a poor outcome. This study compares the 6 month angiographic and long term clinical outcome of long SI in patients (pts) with stable angina, randomized to SI with intravascular ultrasound (IVUS) guidance (group U) or angiographic guidance (group A). Methods: stenoses >20 mm in length and a reference diameter (D) >2.75 mm were eligible. IVUS criteria for optimal SI were: complete apposition, minimal lumen D (MLD)>80% of (proximal + distal reference D)/2 and minimal residual lumen area > distal reference area. Results: In 150 pts (group U, n=74, group A, n=76) a total of 187 stents were implanted. Baseline data were comparable in both groups. All IVUS criteria were achieved in 65 (89%) of group U. Quantitative angiography showed no differences between the groups with respect to baseline (2.9±0.3 vs. 3.0±0.5 mm) post-stent (3.0±0.3 vs. 3.2±0.4 mm) or follow up (2.7±0.4 vs. 2.8±0.3 mm) reference D. The MLD as well as D stenosis before (0.9±0.2 vs. 0.9±0.3 mm/66±14 vs. 69±10%) and after stenting (2.9±0.2 vs. 2.9±0.2 mm/10±6 vs. 11±9%) were also comparable. At 6 months the MLD and D stenosis in group U (1.8±0.4 mm/ 34%) were more favorable than in group A (1.4±0.3 mm/48%; both $p<0.05$). Restenosis (>50%) was found in 9 pts of group U (18%) and in 18 pts of group A (36%; $p<0.05$). The target lesion revascularization rate at 6-months was 4% (n=2) in group U and 21% (n=11) in group A ($p<0.05$), whereas 5 pts (10%) had an intervention for a non-target lesion in both groups (NS). No pts of group U died or had a myocardial infarction within 6 months, but of group A, 1 pt (2%) died and 2 pts suffered an acute myocardial infarction during the 6-month follow up period. Major cardiac events occurred in 8 pts (15%) of group U and in 18 pts (37%) of group A ($p<0.05$) within 6 months. Long term follow up (mean 310±30 days) revealed a target lesion revascularization rate of 8% (n=6) in group U vs. 25% (n=19) in group A ($p<0.05$). Non-target lesion revascularizations were done in 8% (n=6) of group U and in 1% (1 pt) of group A >6 months after the intervention (NS). The long term major adverse cardiac event rate was 18% in both groups (NS). Conclusion: This prospective randomized study shows that 6-month angiographic and clinical outcome after IVUS guided long SI is significantly better compared to angiography guided SI and that this clinical benefit is sustained up to 10 months after the intervention.

P3558 L-arginine and the shear stress response mechanism in diseased epicardial coronary arteries

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Backgroud: L-arginine is the substrate for nitric oxide synthesis and atrial pacing dilates normal epicardial coronary arteries. This study assessed the effects of L-arginine on basal coronary tone and flow-mediated dilation induced by atrial pacing in patients with coronary artery disease and stable angina.

Methods: The effects of an intracoronary infusion of L-arginine 150 μmol/min for 10 mins, was studied in 8 patients with coronary artery disease. In all patients atrial pacing was performed during normal saline and during L-arginine infusion. The luminal diameter of epicardial coronary arteries was assessed by quantitative angiography.

Results: During atrial pacing with saline infusion a significant increase ($p<0.01$ vs. saline) occurred in luminal diameter of the proximal (3.4±0.8%), distal (8.5±1.6%) and stenosis reference segment (5.0±1.2%), but stenosis diameter did not change (0.5±1.5%). L-arginine administration significantly ($p<0.01$ vs. normal saline) increased the diameter of proximal (4.7±1.1%) and distal (6.4±1.4%) segments, coronary stenoses (8.7±2.0%) and their reference segment (6.3±1.6%). However, L-arginine administration did not change (p=NS) the magnitude in mm of atrial pacing induced dilatation from saline or L-arginine respectively in proximal (0.09±0.02 vs. 0.06±0.02 mm) and distal segments (0.12±0.02 vs. 0.09±0.02 mm) and in coronary stenoses (0.01±0.02 vs. 0.02±0.02 mm). A significant correlation ($p<0.001$) was found between % response to nitroglycerin and % L-arginine during atrial pacing.

Conclusions: Non stenotic segments of diseased coronary arteries dilate in response to atrial pacing, but stenoses do not. L-arginine dilates these segments and stenoses but does not increase the magnitude of the response to atrial pacing. These findings provide evidence that the shear stress responsive mechanism is absent at stenoses but present in non-stenotic segments of diseased coronary arteries. They also indicate a relative deficiency of L-arginine, except in the shear response mechanism.

P3559 Coronary artery stenosis assessment – Diagnostic value of contrast enhanced MSCT in comparison with coronary angiography – Pilot study

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Purpose: The present study aimed to compare the diagnostic value of contrast-enhanced Multislice Spiral Computed Tomography (MSCT) for detection of different types of stenoses (>50%, occlusion) in patients with coronary artery disease in comparison with coronary angiography.

Materials and methods: Forty seven patients (28 men and 19 women) with a mean age of 61 SD 12 years underwent MSCT and CA throughout 2000. Patients were included in a retrospective case series study. The examinations were assessed in a blinded fashion, by two separate teams comprised of cardiologists and radiologists. One hundred twenty three out of 186 (66%) proximal and middle segments of left main (segment 5), circumflex artery (segments 11,12), left anterior descending artery (segment 6,7), right coronary artery (segment 1,2) had no significant stenosis, 14 segments (7.5 %) were occluded, and 49 (26%) had significant stenosis > 50%, as determined by CA.

Results: Twenty three (12.3%) segments were unevaluable by MSCT due to poor quality of visualization. Sensitivity and specificity in the evaluable segments were 79% (95% confidence interval, 71% to 89%) and 83% (95% confidence interval 76% to 87%) for > 50% stenosis, and 100% (95% confidence interval, 96% to 100%) for occlusion. There were no differences between MSCT and CA in the detection of occlusion.

Conclusions: MSCT is a promising instrument in non-invasive screening of coronary stenosis and detection of occlusion in proximal part of the arteries. Spatial and time resolution of the method should be enhanced.

P3560 Clinical and angiographic correlates of coronary calcium scoring in multi-slice computed tomography (MSCT)

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The MSCT calcium scoring allows to identify patients with increased coronary event risk or at early stages of coronary artery disease (CAD).

The aim of the study was to find the correlation of calcium score with various clinical features and degree of coronary stenosis.

Methods: 40 consecutive patients (10 women) with angiographically proven coronary artery disease were assessed for coronary calcium score by means of MSCT not later than 48 hours after the angiography. The acquisition parameters were as follows: 3.2 mm slice thickness, 1.6 mm increment, pitch 1.25, 120 kV, 200 mAs, rotation time of 500 ms, supine patients during single breathhold. The calcium score was semiautomatically calculated taking into account the size and density higher than 130 Hounsfield units. The clinical features such as the presence of hypertension, diabetes, dyslipidaemia, obesity (body mass index), smoking, CCS angina score, previous myocardial infarction, CAD duration, degree of stenosis and diffused disease were also analysed by means of Spearman's test.

Results: The calcium score in the left anterior descending artery (LAD) 271±598 showed good correlation with the degree of stenosis in the LAD 69±37 (R=0.591, $P<0.0001$) and angina score (median 2, $P<0.001$). It was also correlated as well as calcium score in the LMS 55±147 with the CAD duration of 9±9 years and diabetes ($P<0.01$). The CS in the RCA 102±362 was associated with the diabetes, dyslipidaemia and obesity with the $P<0.03$. The score in the LCX 282±797 was correlated with the degree of stenosis in every artery ($P<0.001$ for the LCX=56±39). The total calcium score 675±1462 was associated with the angina score, CAD duration ($P<0.001$), diffused disease and the stenosis in the LAD and LCX ($P<0.0001$).

Conclusion: The total and the LAD coronary calcium score may be associated with the severity of symptoms, degree of stenosis in the LAD and disease extent. The calcium deposits in the RCA may be more frequent in patients with metabolic disorders.

P3561 Gadolinium based coronary angiography in patients with chronic renal insufficiency

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Background: Coronary artery disease is one of the leading cause of death in patients with chronic renal insufficiency(CRI). Coronary angiography with injection of iodinated contrast material remains to date the only recognised means to assess coronary anatomy. However iodine, particularly in patients(pts) with CRI, can cause an acute reduction in renal function leading to substantial morbidity and mortality. Gadolinium is a contrast agent believed to be less nephrotoxic than iodine. The aim of our study was to evaluate the safety and accuracy of gadolinium used as an alternative contrast agent in coronary angiography

Methods: We studied 12 pts (mean age 63±9 years- male 8 - 4 with diabetes) with CRI(including 4 pts with a renal graft) referred for coronary angiography because of: angina pectoris n=5, acute coronary syndrom n=4, left ventricular dysfunction n=3. Angiography was performed using the standard judkins technique with 5 or 6 french catheter. A total volume of 45 mL of gadolinium was allowed. Quality of the angiograms obtained was assess by two experienced physicians. After the procedure pts were monitored 48 hours for: cardiac rhytmn abnormality, cardiac troponin I release and, serum creatinine concentration.

Results: No intraprocedural adverse event occurred.Quality of the angiograms was judged sufficient in 10 pts avoiding any significant amount of iodine. In two cases the operator had to switch to iodinated contrast agent. Mean serum creatinine value was 311±110 μmol/L at baseline and 328±149 at H48(p=NS). Only one patient(who received iodine)had an acute renal failure leading to dialysis. No arrhythmias or cardiac troponin I elevation was observed

Conclusions: gadolinium based coronary angiography is feasible and safe in a majority of pts with CRI

P3562 Diagnostic value of electrocardiogram-gated reconstruction by MSCT in assessing patency of arterial and venous coronary artery bypass grafts

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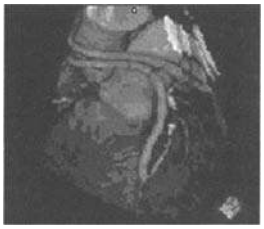
The present study aimed to analyse the diagnostic value of contrast enhanced MSCT for non-invasive assessment of venous and arterial bypass graft patency.

Material and Methods: Study group consisted of 84 patients (27 women) age 42-75 years; mean age 62±10 years who had received venous or arterial bypass grafts. Overall, 235 bypass grafts (26 arterial, 209 venous) were implanted: 65 venous to right coronary artery (RCA), 71 venous and 26 arterial to left anterior descending artery (LAD), and 73 venous grafts to circumflex artery (Cx). MSCT scans (Somatom Plus Volume Zoom, Siemens, Erlangen, Germany) were obtained using Heart View software. Images were acquired throughout the entire cardiac cycle and then reconstructed at diastole with retrospective ECG gating. MSCT scanning and coronary angiography were performed by two separate teams and evaluated in a blinded fashion.

Results: By MSCT 165 grafts, including 147 venous and 18 arterial, were identified as patent and 70 grafts (62 venous and 8 arterial) were diagnosed as occluded, or had significant stenosis (>50%). Bypassography revealed 169 patent (149 venous and 20 arterial) and 66 occluded, or significantly stenosed grafts (60 venous and 6 arterial).Eight bypass grafts (2 arterial and 6 venous: 4 to LAD and 2 to Cx), considered as occluded by MSCT, were patent by conventional bypassography. Four bypass grafts considered as patent by MSCT were occluded in bypassography (1 to LAD, 2 to Cx, 1 to RCA). The specificity and sensitivity of MSCT in detection of graft occlusion was 94.7% and 96.4%, respectively.



CABG to LAD and Mg

Conclusion: MSCT is a valuable instrument in evaluation of bypass patency in patients after surgical treatment of coronary artery disease. MSCT may also be effective in screening patients after CABG procedure.

BRACHYTHERAPY, COATED STENTS

P3563 IVUS dosimetry for intracoronary beta brachytherapy after stenting – What should be the target?

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Background: It seems not to be clear whether the cells responsible for neointimal growth after stent deployment are recruited from media or adventitia. In this latter case the recommended prescription dose for P-32 beta centered source used in Guidant Galileo Brachytherapy System (20 Gy 1 mm beyond the lumen surface, based on angiographically measured artery mean reference diameter) may not have expected effect on reduction of restenosis rate (RR).

Methods: To test the hypothesis whether dosimetry based on IVUS could influence the clinically driven target vessel revascularization (TVR) rate at 6 months we compared two groups of pts, in whom reference diameter (RD) was measured at two different points of reference: 1) 1mm beyond lumen surface (LARD-IVUS)/20 Gy-aimed at media, 17 pts and 2)1 mm beyond the external elastic lamina (EEL) surface (EELRD-IVUS)/20 Gy-aimed at adventitia, 16 pts. In the LARD-IVUS group were 10 pts with in-stent restenosis (ISR), 1 pt with restenosis after balloon angioplasty and 6 pts after elective stenting of de novo (DN) lesions. In the EELRD-IVUS group were 7 pts with ISR and 9 pts after elective stenting od DN lesions. Both groups were well matched in regard to demographic, clinical and angiographic parameters. In each individual pt doses at luminal surface (LS) and 1mm beyond the EEL surface (EEL+1) were calculated.

Results: LS dose for LARD-IVUS group was 60.01±2.44 Gy vs 115.68±33.02 Gy in EELRD-IVUS group, p<0.0001. EEL+1 dose for LARD-IVUS group was 11.46±4.64 Gy vs 20.0±0 Gy in EELRD-IVUS group, p<0.0001. Despite the escalation of the radiation dose in EELRD-IVUS group (93% increase of LS dose and 75% increase of EEL+1 dose) both pt groups have comparable numbers of MACE at 6-month follow-up. There were no death, 1 subacute stent thrombosis followed by QMI and 3 clinically driven TVR in each pt groups. 16 pts (6-LARD-IVUS, 10-EELRD-IVUS) had IVUS follow-up study with volumetric analysis at 6-month. The only difference found was lack of neointimal hyperplasia in LARD-IVUS in comparison to EELRD-IVUS group (delta% change: -0.73% vs 3.64%, p=0.042)

Conclusions: There were no difference in clinically driven TVR rate at 6-month between two pt groups with dose prescription aimed at two different targets within the vessel wall. However, lack of neointimal hyperplasia at 6-month in vessels irradiated with dose of 20 Gy/1 mm beyond the luminal surface is promising and may result in lower TVR rate at 6-month – this should be verified in a large sample study.

P3564 Repeat coronary brachytherapy for recurrent in-stent-restenosis

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Background: Vascular brachytherapy (VBT) is an effective treatment option for in-stent-restenosis (ISR). Nevetheless, the reported target vessel revascularization rate (TVR) after VBT varies between 17 and 33%.

Methods: From 1999 on, repeat VBT is proposed to patients with recurrent ISR after initial successful beta irradiation. Procedures all concern beta irradiation, intervention and dosimetry are guided by intravascular ultrasound and systematic 6 months angiographic follow-up is performed.

Results: From July 1998 on, VBT has been performed in 224 patients at our institution (189 cases of ISR). 11 patients with recurrent ISR have been treated by re-VBT between 25.11.1999 and 16.10.2001. Mean age was 60±6.8 years and 9 patients were male. Vessel type was: LAD (3 pts), RCA (5 pts) and Lcx (3 pts). The pattern of ISR (first, recurrent presentation,respectively) was: focal (4, 4 pts), diffuse (7, 5 pts) and total occlusion (0, 2 pts) with a probably geographical miss in 2 cases at the second restenosis. Clinical recurrence occurred on average at 7±1.9 months the second time. All pts had been treated by beta irradiation with an initial dose of 23.3±3.7Gy and were treated a second time by beta irradiation with a second dose of 25.3±2.2Gy. During the second intervention, no patients received additional stents and evident geographical miss was not noted. All second procedures were performed with the betacath 5F system (Novoste, Brussels, Belgium). The actual follow-up time is 12 ±8 months. At present, a major adverse event occurred in one patient only (CABG for significant non target vessel disease with absence of restenosis at radiation site at 4 months). 6 months repeat angiography has been performed in 7 patients showing absence of restenosis with an average diameter stenosis of 19 ±12%. Currently, all patients are symptoms free on a combined clopidogrel-aspirin therapy to be maintained for at least one year.

Conclusions: These preliminary data show the feasibility of re-beta VBT for recurrent ISR but await further confirmation of its efficacy during a longer follow-up period and by larger patients series.

P3565 External beam irradiation to prevent recurrent coronary in-stent restenosis after balloon angioplasty – A CT based, 3D rendered approach

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Background: Diffuse proliferative in-stent restenosis (ISR) is still a therapeutic challenge. Endovascular brachytherapy can reduce the recurrence of ISR. We hypothesized that selective external beam irradiation may also reduce the reccurrence rate of ISR.

Methods and Results: Twelve symptomatic patients with diffuse, proliferative ISR underwent quantitative coronary angiography (QCA) with subsequent percutaneous transluminal coronary angioplasty (PTCA). Following PTCA, intravascular ultrasound was performed to assess the neointima and media area of the stenotic segment. All patients underwent selective external beam irradiation (total dose: 15 Gy, 5 Gy/fraction, day 1-3, first fraction within 24 hours from PTCA). Irradiation treatment was planned by a true 3D conformal treatment planning system (TMS, Helax). Three or four wedged 5-18 MV photon or cobalt beams with individual absorbers or multi-leaf collimators were used for irradiation. Dose calculations were performed according to the ICRU-Report 50. After six months a control QCA including intravascular ultrasound was performed. The diameter of ISR was 81 ± 1.3% of the reference diameter, decreased significantly after PTCA to 24 ± 0.8% and remained constant 6 months after PTCA (27 ± 1.5% ($p < 0.005$)). Neointima area within the stent was 3.0 ± 0.2 mm^2 immediately after PTCA and remained unchanged after 6 months (2.9 ± 0.2 mm^2). Media area was 7.9 ± 0.5 mm^2 directly after PTCA and was also unchanged at the six month follow up with 7.6 ± 0.4 mm^2. Only one patient showed a significant ISR of 68% accompanied by recurrent angina needing further revascularisation. All other patients were free of clinical symptoms.

Conclusion: Selective external beam irradiation is feasible to prevent restenosis after PTCA of ISR. It can be done on a computed tomography guided, 3D rendered basis and provides a selective noninvasive approach for the irradiation of coronary arteries.

P3566 Stent implantation prior to intracoronary irradiation in instent lesions does not affect the incidence of restenosis

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Background: Stent deployment prior to intacoronary irradiation is recently being debated since publication of trials with poor results in the stent group. In this analysis we aimed to determine if pre-irradiational stent implantation in instent lesions has negative effects on the incidence of restenosis at follow up.
Methods: Interventional data of 93 vessels in 92 patients undergoing revascularization of instent lesions with adjunct intracoronary irradiation and succeeding six-months Clopidogrel treatment were prospectively selected and analyzed. Follow-up percent diameter stenosis was measured with a quantitative coronary angiography edge-detection algorithm (ACOMPC, Siemens). Binary restenosis was defined as %DS >50% within the target vessel.
Results: 48 lesions were localized in the left anterior descending coronary artery, 18 lesions in the left circumflex coronary artery, 25 lesions in the right coronary artery and 2 lesions in bypass grafts. Sr/Y-90 treatment was performed in 46 vessels, P-32 treatment in 31 vessels, and Ir-192 treatment in further 16 vessels. Stents of 3.2±0.5mm diameter and 16.7±7.8mm length were implanted in a total of 32 (34.4%) vessels during the revascularizaion of the instent lesion prior to intracoronary irradiation. Binary restenosis occurred in 27 (31.9%) vessels within a follow-up period of 6.9±2.2 months. Thrombus associated total occlusions were found in 2 patients who have had stent implantations, and in further 2 patients who have had balloon treatment only (6.25% vs. 3.51% respectively; p=0.54). Stent implantation during the revascularizaion of the instent lesion did not lead to higher incidence of binary restenosis than balloon treatment alone without stent deployment (25.0% vs. 35.7% respectively; p=0.29).
Conclusion: Stent implantation prior to intracoronary irradiation in instent lesions with adjacent six-months Clopidogrel treatment is not associated with higher restenosis rates at follow up.

P3567 The degree of residual stenosis does not impact the long-term outcome of patients treated for in-stent restenosis with brachytherapy

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Background: Vascular brachytherapy (VBT) demonstrated efficacy in the reduction of recurrence of in-stent restenosis (ISR). However, the importance of minimal residual stenosis of the angioplasty preceding VBT has not been established in patients with ISR.
Methods and Results: 368 patients were treated for ISR in native coronary arteries with gamma-radiation in the WRIST (Washington Radiation for In-Stent Restenosis) series. Patients had conventional angioplasty followed by 192Ir radiation. Quantitative coronary angiography was performed at the index procedure with subsequent 6-month angiographic and clinical follow-up. Patients were classified in three groups according to the residual stenosis (RS) after the index procedure: optimal angiographic result (RS<20%, n=45), sub-optimal angiographic result (RS=20-30%, n=85), and incomplete angiographic result (RS>30%, n=211). The late loss was higher in the optimal and sub-optimal angiographic result groups than in the incomplete angiographic result group (respectively 0.65 ± 0.65 mm, 0.56 ± 0.73 mm and 0.32 ± 0.65 mm, p=0.003). The 6-month clinical outcome was similar in the three groups. Major cardiac event rates were 30% in the optimal angiographic result group, 32% in the sub-optimal angiographic result group, and 26% in the incomplete angiographic result group (p=0.47). Multivariate regression analysis shows that the residual stenosis and the post-procedure MLD were not predictors of TVR at 6 months, when RS was considered a continuous variable.
Conclusions: An optimal result of the angioplasty procedure does not influence the angiographic and clinical outcome of patients undergoing VBT for the treatment of ISR.

P3568 Angiogenesis and intraparietal haemorrhages are the major long-term effects of intravascular gamma-radiation after stenting in rabbit arteries

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Background: Experimental data on the long term effects of Intravascular Brachytherapy (IVB) associated with stenting are limited. Recent clinical trials showed adverse events after IVB, in particular thrombosis occurring at long term follow-up. In the present study, we examined the late outcome of rabbit stented arteries after IVB, in particular neovessels formation. Methods: Stents (Bestent, Medtronic) were implanted in arteries of 32 male N-Z rabbits and immediately followed by gamma IVB using an afterloading device (Nucletron) or sham radiation procedure. High dose rate 192 I source delivered 18 Gy at 2 mm from the source centre. The animals received ticlopidine for 30 days. At 1 and 6 month follow-up, arteries were harvested for histomorphological and immunohistochemical analysis. Results: No significant difference in intimal area was observed between the control and the irradiated group at 1 and 6 months (respectively 1.26 ± 0.09 vs 1.02 ± 0.2 mm^2, ns and 1.07 ± 0.17 vs 1.32 ± 0.47 mm^2, ns). In contrast, intramedial haemorrhages (free hemosiderin deposition) and inflammation (presence of macrophages) were only observed in radiated arteries. In IVB group, Von Willebrand labelling showed adventitial and intra-medial neovascularization at 6 month follow-up confirmed by neovessels count in radiated vs control arteries (respectively 5.05 ± 1.04 vs 1.51 ± 0.27/mm^2, p<0.001). Conclusion: Our study strongly supports the hypothesis that IVB associated to stenting induced late arterial wall neovessels formation and intraparietal haemorrhages. Whether the rupture of these fragile neovascular structures could lead to late occlusions described at long term follow-up in clinical trials remains to be elucidated.

P3569 Failure of prevention of vein graft disease by prophylactic gamma radiation in a chronic hypercholesterolemic porcine model

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Background: The value of brachytherapy in preventing neointima formation and vessel occlusion in proliferating healthy vessels, such as vein grafts, is unknown. We studied the effect of gamma radiation on vein graft patency, vessel wall diameters, platelet-derived growth factor (PDGF) expression, and smooth muscle cell (SMC) proliferation/cell death in a chronic hypercholesterolemic porcine model.
Methods and Results: Carotid artery jugular vein bypass grafts were anastomozed end-to-side in 23 pigs after ex-vivo irradiation of the vein grafts (10, 20 and 40 Gy). 16 native vein grafts served as controls. Quantitative expression of PDGF-AA and -BB was assessed using ELISA, quantitative SMC proliferation/cell death with double-stain immunohistochemistry (Mib-1/TUNEL/SMC a-actin). Computer-aided planimetry was used for morphometric analysis. The in-vitro response of endothelial vasodilatation in veins irradiated with 40 Gy was examined.
Planimetric data on vessel wall dimensions revealed no positive effect of gamma radiation on neointima formation and inner lumen diameter. On the contrary, vein grafts subjected to 40 Gy were significantly more likely to be occluded and to have reduced inner lumen and increased neointima formation. Radiation therapy had no effect on PDGF expression and SMC proliferation/cell death. The mean inner lumen diameter decreased as PDGF-AA expression increased. Vasodilation induced by acetylcholine was unaffected.
Conclusions: Prophylactic gamma radiation of unaffected vein grafts failed to prevent vein graft disease in a hypercholesterolemic porcine model. High-dose radiation (40 Gy) resulted in more frequent graft occlusion and vein sclerosis. PDGF values and SMC proliferation/cell death were unaffected by radiation.

P3570 Sirolimus inhibits restenosis irrespective of the vessel size. A subanalysis of the multi-center RAVEL trial

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Vessel size is an established predictor of angiographic outcome after catheter-based intervention. Neointimal growth is a uniform vascular reaction to vessel injury. Higher relative neointima growth (with respect to vessel caliber) is considered responsible for the unfavorable outcome in small vessels.
We investigated the relationship between vessel size and late lumen loss after implantation of sirolimus eluting stents.
Pts with single de-novo lesions were randomized to receive a 18mm sirolimus eluting (SES) BX velocity™ stent (Cordis, Waterloo, Belgium) or a bare 18mm BX velocity™ (BS) stent (Cordis, Waterloo, Belgium). QCA was performed at baseline and at 6 month follow-up (fup). Vessels were stratified according to their diameter (RD) terciles. Late lumen loss (LL) was calculated as "MLD post procedure (post) - MLD fup".
Results:

Stratum	Parameter	SES	BS
I	n	37	38
	RD (mm)	2.05 ±0.20	2.08± 0.21
	MLD post (mm)	2.03 ±025	2.07± 0.29
	MLD fup (mm)	2.05 ±0.32	1.22± 0.46
	LL (mm)	-0.01± 0.25	0.85 ±0.52
II	n	40	38
	RD (mm)	2.53 ±0.14	2.61± 0.14
	MLD post (mm)	2.38 ±0.28	2.39± 0.26
	MLD fup (mm)	2.35 ±0.39	1.68 ±0.45
	LL (mm)	0.03± 0.34	0.79 ±0.51
III	n	39	38
	RD (mm)	3.21± 0.39	3.22 ±0.29
	MLD post (mm)	2.80± 0.28	2.72 ±0.29
	MLD fups (mm)	2.83 ±0.36	1.97± 0.55
	LL(mm)	-0.04 ±0.25	0.76 ±0.58

The classical negative relation between vessel size and late lumen loss was seen in the bare stent group, but not in the sirolimus eluting stent group. Sirolimus eluting stents prevent neointimal growth and late lumen loss irrespective of the vessel size.

P3571 Local delivery of paclitaxel to prevent recurring, diffuse in-stent restenosis

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It has been proved in animal model that paclitaxol has cytotoxic influence on intimal cells. Therefore, the aim of this study is to test weather locally delivered paclitaxol can prevent recurrence of diffuse in-stent restenosis.
Methods: Five patients with at least two episodes of in-stent restenosis within the same coronary segments were included to the study. Eleven restenotic segments underwent pre-dilatation with Remedy balloon catheter. At the end of the first dilatation 100ìg of paclitaxol diluted in 2 cc of 0.9% NaCl was delivered into the artery wall under the pressure of 2-3 atm during 60 s in each place. Post-dilatations with larger balloon was performed to gain optimal result. No additional stenting was required in any case. There was no major acute coronary events during hospitalization and 6 month observation. Blood tests performed one and four weeks after the procedure did not reveal any abnormalities which could be connected to cytostatic treatment.
Follow-up angiographic evaluation showed late loss of 0.4±0.5 mm and restenosis in 3 segments (27.2%). Repeat angioplasty with delivery of increased dose of paclitaxol (200 ìg in 2 cc) was performed in three patients with restenosis. The late results will be known after next six months.
Conclusions: Locally delivered paclitaxol might be valuable treatment of in stent restenosis, however further evaluation of a proper dose of delivered drug is warranted.

P3572 Evaluation of incomplete stent apposition at six month follow-up in the multi-center RAVEL trial

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The incidence of incomplete stent apposition(ISA) has been recently reported between 12 and 17% immediately after stent implantation.Most of the ISA resolve at 6m FU. The objective of this study was to quantify and investigate the incidence of ISA as well as its clinical implication in the RAVEL trial.
Methods: A subset of pts included in the RAVEL trial whom IVUS was performed (n=95)at 6m FU were investigated. Pts with single de-novo lesions were randomized to receive 18mm Sirolimus eluting stent(SES) and uncoated BX-Velocity stents(UCS).ISA was defined as >1 strut clearly separated from vessel wall with evidence of blood speckles behind the strut.The incidence of ISA was established based on the consensus of three independent analysts.
In pts who had ISA, the number of areas of ISA per stent were determined from cross sectional IVUS images.The total length of ISA were calculated by number of frames involved.The maximal number of struts separated from the vessel wall,the maximal depth (distance between the most separated strut and the vessel wall)and the maximal circumferential extent of ISA(angle)are reported.Finally,the volume of the ISA was quantified.
Results: Two groups revealed similar ISA characteristics in quantitative analysis (table). The event free survival rates at 1 yr was 98% in the SES grp vs 72% in the UCS grp. The 10 pts with ISA in SES grp were event free at 1yr while 1 pt in the UCS grp underwent re-PTCA.

Characteristics of ISA

	SES	UCS
Frequency (%)	(21) 10/48	(4) 2/47*
Number of ISA per stent	1.9± 0.6	2
Max. number of struts	3.6 ±0.97	4.0 ±1.41
Total length(mm)	6.7± 3.7	6.9 ±2.2
Max.Depth(mm)	0.75 ±0.33	0.62 ±0.08
Max.Angle	154 ±68	131± 38
Volume of ISA	20 ±24	27± 16
Stent Volume	131±35	132±36

*p<0.001

Conclusion: The incidence of ISA in pts with SES is higher than with UCS at 6M FU. In the SES grp no sub-acute or late (1yr) adverse event was associated with ISA detected at 6M. Long-term follow-up migt be necessary to establish the significance of this phenomenon.

P3573 Sirolimus-eluting stents suppress neointimal proliferation irrespective of the amount of residual plaque burden

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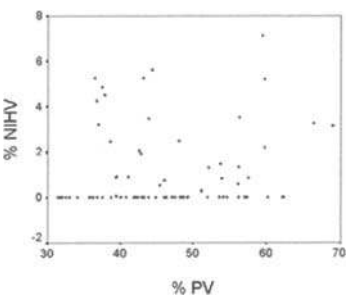
Background: The correlation between residual plaque burden after conventional stenting and neointimal formation has been previously reported. However, it has not been established whether this phenomenon is seen as well in drug-eluting stents. In addition, the pharmacological kinetics (elution, diffusion, ...) might be affected by the amount of plaque burden (cell contents).
Methods: 15 patients who received an 18 mm sirolimus-eluting Bx VELOCITY stent (Cordis, Waterloo, Belgium) and intravascular ultrasound (IVUS) examination with a motorized pullback after stenting and at 6-month follow-up were included in this 3D IVUS analysis. The stented segments were divided into six subsegments. The following IVUS measurements were obtained in each subsegment: external elastic membrane volume (EEMV), stent volume (SV), lumen volume (LV), % plaque volume behind stent (PV) calculated as 100*(EEMV-SV)/EEMV, % neointimal hyperpasia volume (NIHV) calculated as 100*(SV-LV)/SV.
Results: Complete analysis was possible in 76/90 subsegments (14 subsegments were excluded because of calcification which precluded the quantification of EEMV). No significant correlation between %PV after stenting and %NIHV was found (figure). %NIHV in the subsegments (n = 24) with %PV > 50 was similar to that in the subsegments (n = 52) with %PV < 50 (1.3 ± 1.9%, 0.9 ± 1.7%, respectively; p = 0.41).



Conclusion: The plaque burden behind a sirolimus-eluting stent does not correlate with neointimal formation, supporting the fact that sirolimus elution from stent suppresses NIH irrespective of the amount of residual plaque burden.

P3574 Cost-effectiveness of the sirolimus eluting Bx-VELOCITY stent: 1-year results

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Background: The RAVEL study showed excellent efficacy results in favor of the Sirolimus eluting Bx-VELOCITY stent(CYPHER) when compared to non-eluting stents. However, when using these stents, costs may increase and questions may arise about the balance between the additional costs and effects.
Methods: In the RAVEL trial, an international randomized clinical trial in patients with single vessel disease, 120 patients were randomized to CYPHER and 118 patients were included in the control arm. Data about resource utilization was collected alongside the trial and costs are calculated by multiplying resource utilization with unit costs from The Netherlands. The cost of CYPHER was set at EUR 2,000. Effectiveness was defined as freedom from composite death, myocardial infarction and target lesion revascularization (MACE free).
Results: Except for the cost of stents, the procedure cost in both treatment arms were similar leading to a net difference in procedure cost of EUR 1,274 (EUR 4,451 vs. EUR 5,725). Due to the decreased need for repeat-revascularizations (1 vs. 28) the percentage patients MACE-free differed in favor of the Sirolimus eluting stent with 23.0% (71.2% vs 94.2%). As a consequence, follow up cost differed significantly (EUR 3,568 vs. EUR 2,072) and after 12 months the higher procedure cost in the Sirolimus eluting stent group were more than compensated by the savings in follow-up costs (p=0.01).
The cost-effectiveness analysis showed dominance of CYPHER over the bare stent (better effectiveness in combination with cost savings). The upper limit of the 95% confidence interval considering the costs per additional MACE-free survivor was estimated at EUR 5,237.
Conclusions: This study shows that, after 12-month follow-up, CYPHER is both more effective (94.2% vs. 71.2% MACE free) as well as less costly (EUR 7,796 vs. EUR 8,019). This, together with the upper 95% limit concerning cost effectiveness suggest that using CYPHER is a cost-effective treatment option in the type of patients as selected for this study.
Please note that these data are preliminary. Final data will be presented during the congress.

P3575 Quinaprilat coated PC stents do not attenuate intimal thickening in a porcine coronary model

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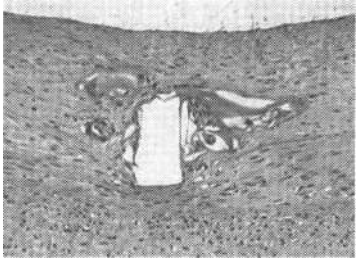
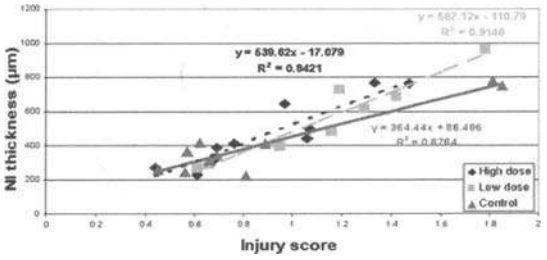
Introduction: ACE inhibitors such as quinapril are known to inhibit smooth muscle cell proliferation. In addition, quinapril has matrix metalloproteinase inhibitor activity which is also postulated to attenuate intimal thickening. Our objectives were therefore to evaluate the performance characteristics of PC coated stents loaded with 800 μg quinaprilat (Q) and it's solvent dimethylacetamide (S) in comparison to coated but not loaded control stents (C) in normal porcine coronary arteries.
Methods: Ten animals received both a Q, S and C under guidance of QCA. They received 300 mg ASA and 75 mg Clopidogrel daily until sacrifice at 4 weeks. Arteries were harvested for histology and morphometry with stents in situ.
Results: QCA revealed a balloon-artery ratio of 1.0±0.1, 1.1±0.1 and 1.1±0.1. Late loss was 0.23±0.26, 0.25±0.3 and 0.05±0.3 for Q, S and C (p=NS). Morphometry revealed neointimal areas of 2.6±1.1, 2.1±0.6 and 1.9±0.5 mm^2 and intimal thicknesses of 0.4±0.1, 0.3±0.05 and 0.3 ±0.1 mm for Q, S and C. While late loss and intimal area are smaller for the control group, statistical analysis showed no significant differences, even when taking balloon-artery ratio or histological injury scores into account. Microscopy showed no qualitative differences between the three groups, all containing a minimal to moderate but asymmetrical neointima. Endothelialization was complete but leucocyte adhesion was observed in all groups, as were macrophage giant cells surrounding stent struts and coating remnants (figure).
Conclusion: Quinapril given locally in a concentration of 800 μg per stent has no significant influence on intimal thickening at four weeks following stent placement in normal porcine coronary arteries.



P3576 Simvastatin coated PC stents do not attenuate intimal thickening in a porcine coronary model

H.M.M. Van Beusekom, E. Regar, S. Visser-van der Veer, M. van Dullemen, S. Rodjan, M.G. Punt, M. Harteveld, W.J. van der Giessen. *Erasmus Medical Centre Rotterdam, Cardiology Dept., Rotterdam, Netherlands*

Introduction: Intermediates of cholesterol biosynthesis are essential for cell growth and drugs affecting this metabolic pathway are potential anti-restenotic agents. Inhibitors of HMG-CoA reductase such as statins fall into this category and have shown antiproliferative properties in vitro. Statins can also improve endothelial function. Our objectives were therefore to evaluate the performance characteristics of PC coated stents loaded with a high (H, 100 μg) and a low dose (L, 30 μg) of Simvastatin in normal porcine coronary arteries in comparison to not loaded control stents (C).
Methods: Animals (n=10) received both a H, L and C under guidance of QCA. They received 300 mg ASA and 75 mg Clopidogrel daily until sacrifice at 4 weeks. Arteries were harvested for histology and morphometry with stents in situ.
Results: QCA revealed a balloon-artery ratio of 1.05±0.1, 1.18±0.1 and 1.15±0.1 for H, L and C (p<0.05 H vs. L). Morphometry showed no statistically significant difference in neointimal area in the three groups (3.4±1.7, 4.0±1.6 and 2.8±1.6 mm^2 for H, L and C). Regression analysis for injury vs neointimal thickness showed no difference in the slope (Figure I).
Microscopy revealed a marked asymmetrical but endothelialized neointima. The degree of cellularity of the intima was similar between the groups and only in instances of extensive NI thickening was the relative proportion of extracellular matrix increased. All arteries contained macrophage giant cells surrounding stent struts and coating remnants.



Conclusion: Simvastatin given locally using the drug delivery BiodivYsio PC stent at 30 and 100 μg per stent does not have a significant influence on intimal thickening at four weeks following stent placement in normal porcine coronary arteries.

P3577 Synergistic effects of a novel nanoporous stent coating and tacrolimus on intima proliferation in rabbits

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Background: To overcome the problem of in-stent-restenosis the concept of local delivery of antiproliferative or immunosuppressive drugs has been introduced into interventional cardiology. Local drug delivery can be achieved by drug-eluting-stents coated with polymer surfaces used for controlled drug release. However, several polymer coatings have shown an induction of inflammatory response and increased neointima formation. In contrast, inorganic coatings have been shown to reduce intima proliferation, but are normally not suitable for sustained drug release. In the present study the effect of a new ceramic nanoporous aluminum-oxide (Al2O3) coating on neointima proliferation and its suitability as a carrier for the immunosuppressive drug tacrolimus (FK506, Fujisawa Pharmaceuticals Co., LTD., Japan) has been investigated.
Methods: 316L stainless steel coronary stents were coated with a 500 nm thin nanoporous aluminum-oxide layer. This ceramic nanolayer was used as a carrier for the anti-proliferative and anti-inflammatory drug tacrolimus. Bare stents (n=6), ceramic coated stents (n=5), ceramic coated stents with 60 mg (n=6) and 120 mg (n=6) tacrolimus loading were implanted in the common carotid artery of New Zealand rabbits.
Results: The ceramic coating caused a 42% reduction in neointimal thickness (p=0.16). Loading the ceramic stents with tacrolimus led to a significant reduction of neointima thickness by 52% for 60 mg (p=0.047) and 60% for 120 mg (p=0.036). The ceramic coating alone as well as in combination with tacrolimus showed a reduced infiltration of lymphocytes and macrophages in response to stent implantation than the bare stents.
Conclusion: Ceramic coating of coronary stents with a nanoporous layer of aluminium oxide results in a significant reduction in neointima formation and inflammatory response. The synergistic effects of the ceramic coating and tacrolimus suggest that this new approach may have a high potential to translate into clinical benefit.

P3578 Stent coating alone with n-butyl methacrylate induces apoptosis of smooth muscle cells

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Background: Coated stents can deliver locally drugs in adequate concentrations to inhibit cell proliferation and migration. Several stent coatings have been tested either experimentally or clinically, including heparin, silicon carbide, gold, polymers with and without drug elution, and radioactive coatings. Synthetic polymers, like methacrylate compounds, have been proposed as a solution to improve the quality of stents, to serve as a vehicle for local (high-dose and site-specific) drug delivery, or both. However, the effects of coating alone has non been studied extensively.
Methods: The aim of this study was to evaluate the potential effects of coating alone with n-butyl methacrylate (BMA) on VSMC proliferation in vitro. SMC (A10, thoracic aorta, rat) were grown to ~ 80% confluence in monolayers at 37°C in a humidified atmosphere at 95% air CO2 in 10% FCS-DMEM (fetal calf serum-Dulbecco's modified Eagle's medium) with 4 mmol/liter l-glutamine, 4.5 g/liter glucose, and 1.0 mmol/liter sodium pyruvate. Coating was prepared releasing BMA on the stents, under sterile conditions, at the following concentrations: 0.003μg, 0.03μg, 0.3μg. For growth inhibition experiments, 1 x 10^5 cells were plated into a six-well plate and grown in DMEM 10% FCS in the presence of BMA-coated stents gently added in each well, or in the absence of them (controls).
Results: Cell number in both conditions was assessed at baseline and at 3h, 12 h and 24 h. After 24 hours treatment, apoptosis was detected by fluorescence microscopy using propidium iodide (PI) and annexin V. A significant increase in % of apoptosis was detected after release of coated stents (BMA-coated stent 0.003μg= 68.4% p<0.01, versus controls; BMA-coated stent 0.03μg = 96.1%, p< 0.001 Vs controls; BMA-coated stent 0.3μg= 94.7% p<0.001 Vs CONTROL =7.6%).
Conclusions: Methacrylate coating induced apoptosis in a dose-dependent manner. Thus, methacrylate is biologically active per se, this effect should be taken in account in evaluating an association of this coating with an antiproliferative and antinflammatory agent.

P3579 Effect of autologous vein graft coated stents saturated with combined chemotherapy agents on porcine coronary arteries

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Background: One of the main limitations of stenting is restenosis. The purpose of this study was to investigate the effect of implantation of autologous vein graft coated stents (AVGCS), saturated with a combination of two cytotoxic agents, on intimal hyperplasia in the coronary arteries of 15 pigs (20-25Kg).
Methods: An autologous vein graft was removed from the right front leg of the animal. The boundary tissues of the graft were removed and it was stabilised on the external surface of a new stent which was designed in our Institution. The new stent consists of waveform rings connected by small bridges. Three connecting arms are attached at each edge of the stent and can be rotated by 180° after the placement of the graft, in order to stabilize the graft on the stent. Thereafter, a solution of cis-platinum (0.1mg/0.05ml) and mitoxandrone (0.465mg/0.95ml) was evenly infused into the wall of the vein. Eight AVGCS saturated with cis-platinum and mitoxandrone were implanted to LAD and 7 to LCx. Fifteen unsaturated AVGCS were placed in the other branch of the left coronary artery serving as control group. Balloon to artery ratio was 1.17 ± 0.1. Maximum balloon pressure was 15 atm. At 5 weeks, the animals were sacrificed after completion of coronary angiography and morphometric studies were performed.
Results: All vessels were patent after the implantation and at 5 weeks. No acute or late thrombosis was observed. Histologically, endothelialization was similar between the two groups. The arterial middle layer was thinner in the AVGCS saturated with cis-platinum and mitoxandrone compared to the control group.
Conclusion: The implantation of AVGCS saturated with a combination of cis-platinum and mitoxandrone in porcine arteries is easy and uncomplicated. This is the first study demonstrating that combined cytotoxic drug delivery autologous vein graft coated stents may reduce intimal thickening in this animal model.

PAEDIATRIC CATHETER INTERVENTION

P3580 Four year follow-up of ASD catheter closure with the Amplatzer septal occluder in adults: single center experience in 223 patients

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Purpose: Atrial septal defect (ASD) transcatheter closure has been reported as a suitable alternative to surgery in children and adults. This is a report of the results in one of the world largest series of adult patients.
Methods: Between November 1997 and January 2002, catheter closure of an ASD was attempted with the Amplatzer ASD occluder in 223 consecutive adult patients (mean age 45 ± 17 years; range 13 to 90). These patients had an atrial septal defect with a diameter between 11 and 34.5 mm (21 ± 5 mm). Qp:Qs ranged from 0.8 to 4.2 (2.0 ± 0.7). 15 patients had multiple defects. The systolic pulmonary artery pressure was > 30 mm Hg in 70 patients (31%) and > 50 mm Hg in 20 patients (9%).
Results: The implantation of the device was primarily successful in 222/223 patients. 200/223 procedures could be performed under local anesthesia. The device diameter varied from 12 mm to 40 mm (median 22). The mean procedure time was 46 ± 21 min., the X-ray time 7.8 ± 5.5 min. and the length of hospital stay 0.9 ± 1.1 days. Device embolization occurred in 1 patient (surgery uneventful), pericardial effusion in 1 (asymtomatic) and air embolism in 1 (without clinical consequences). Transesophageal echocardiography showed complete closure after 6 months of the defect without any residual shunt in 218 of 223 patients. 5 small residual shunts disappeared 1 year after closure. During follow-up up to 48 months, another patient developed pericardial effusion (pericardiocentesis successful, no sequelae). One patient suffered from hemopericardium 7 months after device implantation (surgical uneventful). 9 patients developed atrial fibrillation (cardioversion successful in all of them). No thrombus formation could be detected.
Conclusion: After transcatheter closure of an atrial septal defects late complications may occur. However, compared with some older devices this is a reliable and safe procedure with excellent short and mid term results. High closure rates of up to 98% can be achieved. According to the literature these results are superior to surgery.

P3581 Improved interventional closure of patent foramen ovale with the Cardia ASD-Star occluder

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Despite angiographically successful sealing of a patent foramen ovale (PFO) with an implantable occluder, transesophageal echocardiography reveals residual leakage in up to 30%. This applies particularly to small, low metal, double umbrella devices (e.g. Cardia PfoStar®). With the PfoStar® the thin center pin connecting the two umbrellas tends to position itself asymmetrically at the border of the PFO increasing the risk that the foramen is not covered by the umbrella. Possibly one or more wires even cross the foramen, resulting in a considerable leakage.

To overcome this limitation, we implanted a new occluder type, the Cardia ASD-Star® in 20 patients (12 male, 8 female; age 48±14 years) with cerebral ischemia and PFO. Unlike the PfoStar® consisting from 2 polyvinyl-alcohol umbrellas attached to 2 crossed wires connected by a thin metal pin, the ASD-Star® has 3 crossed Nitinol-wires and a tube-like, elastic connection between the umbrellas. In 19 patients cardiac magnetic resonance imaging (MRI) was performed before and after device delivery. MRI included shunt quantification and first-pass perfusion in the atria during valsalva's manoeuvre and anatomical evaluation of the atrial septum and the position of the occluder by cine-MRI in short and long axes.

The mean PFO length (TEE at 150 degrees) was 16.7±3.6 mm (9-24 mm). Before device implantation TEE revealed an inducible atrial right-to-left passage of echo-contrast medium in all patients. MRI before PFO sealing showed in 10 (53%) patients contrast leakage in the septum, and in 4 (21%) patients a quantifiable atrial shunt. Correct placement of ASD-Star device was achieved in all 20 patients. The mean outer diameter of the ASD occluders was 33±3 mm (28-36 mm) with a mean inner diameter of 13±3 mm of (8-20 mm). All patients received ASA and Clopidogrel for 6 months. Following sealing the atrial septum was perfectly closed in 19 patients, without residual shunt detectable by TEE or MRI. Only 1 patient showed in TEE a minor right-to-left leakage at Valsalva's manoeuvre. One patient who had also a non-critical 60% stenosis of the carotid arteria, suffered from a transient ischemic episode during 6-months follow-up.

We conclude, that despite the same outer diameter, centering the umbrella provides an improved covering of the PFO. It prevents dislocation of wires through the PFO, and reduces residual shunts after interventional PFO sealing.

P3582 Catheter closure of patent foramen ovale (PFO) with the Helex occluder: the European experience

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Background: Patients with cryptogenic embolic events and a PFO are at risk to suffer from recurrent cerebral events. We conducted a prospective multicenter trial to evaluate the feasibility of PFO closure with the new Helex occluder (W.L. Gore).

Methods: The Helex Septal Occluder consists of two discs. A nitinol wire frame is covered by expanded polytetrafluoroethylene (ePTEE). The device is introduced, and if necessary retrieved also after complete deployment, via a 9 F delivery catheter. There is no need for using a long trans-septal sheath. The flexible device has a very low profile once deployed. We attempted transcatheter PFO closure in 127 patients in Europe. The age ranged from 15 to 80 years (mean 50 "b 13). These patients suffered from 158 embolic events prior to PFO closure. The streched diameter of the PFO ranged from 3 to 23 mm (mean 10 mm).

Results: The implantation of the Helex Septal Occluder was successfully performed in all patients. Two devices embolized and could easily be retrieved with a snare. The PFO was closed with a second occluder. The device diameter was 15 mm in 34, 20 mm in 53, 25 mm in 27, 30 mm in 10 and 35 mm in 2 patients. The procedure was performed in local anesthesia in 107/127 patients. Mean X-ray time was 10 min., including balloon sizing of the defect. 44 patients showed a residual shunt immediately after implantation by transesophageal echocardiogram (TEE).

Follow-up: After 6 months 10/65 patients had a residual shunt. In one of them this was closed with a second occluder. During follow up (1 to 27 months) no further embolic event occurred. One wire fracture was detected. Atrial flutter could be observed in one patient. The cardioversion was successful.

Conclusion: Compared to other devices this device has soft atraumatic edges. There is no risk of air embolism during implantation. Catheter removal is possible at any stage during or after deployment. The thrombogenity of the device is very low. PFO closure with the Helex occluder is a very safe procedure and prevents further embolic events.

P3583 Advantages and limitations of ASD and PFO closure with the CardioSEAL-STARFlex-occluder: single center experience in 110 adult patients

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Background: The STARFlex occluder is a modified CardioSEAL double umbrella device which provides a self-centering mechanism achieved by microsprings attached in alternating fashion between the opposing arms of the umbrella. The microsprings also lead to a better apposition of the device arms to the septum. **Methods:** Between June 1999 and January 2002 catheter ASD closure (n=32) or PFO closure (n=78) was attempted with the STARFlex occluder in 110 consecutive patients aged from 17 to 77 years (mean 50 ± 14). 17 of the ASD patients had multiple defects. In 11/17 patients two occuders were implanted.The ASD diameter varied between 5 and 20 mm (14 ± 4 mm), Qp:Qs from 0.8 to 4.2 (2.0 ± 0.7). In the PFO patients an atrial septal aneurysm was found in 24%, the PFO diameter ranged from 4 to 17 mm (10 ± 3 mm). 118 embolic events occurred in these patients before PFO closure. **Results:** The implantation of the occluder was successful in 107/110 patients. The device diameter varied from 23 mm to 40 mm (median 24). In 2 patients with 20 mm defects a stable position of the device could not be achieved, it had to be retrieved. In another patient with a 20 mm defect the occluder embolized into the aorta several hours after implantation without causing clinical symptoms. Catheter retrieval was successful. During follow up (0.03 to 32 months) routine 4 week transoesophageal echocardiogram (n=83) revealed a thrombus on the device in 6 patients (7%). Two minor strokes occurred. In two patients the thrombus was removed surgically. No further complications occurred. After 6 months transesophageal echocardiography showed complete closure of the defect in 107/110 patients (97%). No device arm fractures occurred. **Conclusion:** The STARFlex-occluder is suitable for both defects, ASD's and PFO's, even in complex defects like multiple perforations or with associated septal aneurysm. However, the success rate in defects larger than 20 mm is lower, device malposition or embolization may occur. Thrombus formation seems to be relatively high. This should be addressed in the development of future device generations. The advantage of this device is that despite the centering mechanism large devices can be implanted in small defects. Thereby occasionally additional defects can be covered with only one device providing an excellent closure rate.

P3584 Can transcatheter closure of patent foramen ovale be safely and effectively performed without transoesophageal echocardiography?

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Background: The use of transesophageal echocardiography (TEE) during transcatheter closure of patent foramen ovale (PFO) adds significantly to patient discomfort. TEE, particularly when performed with general anesthesia significantly increases procedure time and demands on personal and equipment resources, thus raising costs. Therefore, we studied safety and efficacy of PFO closure without routine use of TEE. **Methods:** After a learning period during which PFOs were closed under TEE surveillance, procedures were performed with fluoroscopy, only. Results were evaluated with right atrial angio and transthoracic echo (TTE) before device release. TEE was restricted to situations where appropriate implantation remained uncertain. Amplatzer PFO occluders were used and the choice between size 25 and 35mm was based on preinterventional TEE studies (PFO size, location, septal aneurysm). Patients received Aspirin 2 days prior to intervention and the following 6 months. TTE was performed 1 day, 1 week, 3, 6, 12 and 24 months after intervention. Echo contrast studies were repeated until complete closure was documented. **Results:** 100 patients (56 female, age 47.6±11.5 years) underwent PFO closure. In one pt. the procedure was terminated before implantation because of technical problems at the groin site, in one pt. no implantation was performed because the PFO presented with such a small fixed channel that predilation would have been necessary and in one pt. no PFO was found and repeat TEE showed that the preinterventional study had been false positive. In the remaining 97 pts, device implantation was successfully performed with a mean total procedure time of 32±11 minutes. Unplanned TEE during the procedure was necessary in only 2 pts (2%). Complications were: pseudoaneurysm requiring surgery (1), uncomplicated coronary air embolism (1), atrial fibrillation with spontaneous conversion (1), AVNR-tachycardia (2). Residual shunt as documented by echo contrast was frequent on the first day (23%) but only present in one pt. at 3 months and in no pt. after 6 months. During a mean follow-up of 291±221 days, one stroke and 4 TIAs occurred. A residual shunt at the time of the event was found in only one pt. One pt. developed multiple sclerosis, one pt. epilepsia. **Conclusion:** These results demonstrate that PFO closure can safely and effectively be performed without routine TEE and, thus, without general anesthesia. However, they also emphasize the dilemma of patient selection for the procedure and the necessity of ongoing randomized trials comparing PFO closure and medical treatment.

P3585 Cardiopulmonary excercise capacity increases in patients with atrial septal defect following transcatheter closure

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Objectives: Hemodynamic abnormalities in adult patients with atrial septal defect (ASD) of the secundum type are associated with exercise limitation. The purpose of the prospective non-randomized study was to evaluate cardiopulmonary exercise capacity and ventilatory function in adults with ASD before and twelve months after transcatheter closure using the Amplatzer septal occluder. Background: There are only few data available on cardiopulmonary exercise tolerance after surgical closure, but nothing about patients after transcatheter closure of atrial septal defects in adults.
Methods: Twenty-three patients (14 women, 9 men, aged 43±13 years) underwent interventional closure of an ASD with an Amplatzer occluder (mean occluder size 24±3 mm, range 15 to 32). The pulmonary-to-systemic flow ratio was >1.5:1 in all patients. No life-threatening procedural complications occurred. Cardiopulmonary exercise testing was performed by supine bicycle ergometry. We determined peak oxygen uptake at anaerobic threshold, maximal performance, oxygen pulse, and the breath volume per minute before and twelve months after interventional closure of the defect.
Results: Peak oxygen consumption at baseline was reduced to 14.2±3.6 ml/min/kg and increased to 16.1±4.5 ml/min/kg after twelve months ($P<0.01$). The increasing in maximal performance from 75±32 watts to 125±30 watts ($P<0.05$) and the oxygen pulse 8.1± 2.2 ml to 10.1± 2.5 ml ($P<0.05$) were also significant. Breath volume per minute increased after twelve month from 27.1±6.2 l/min to 35.3±9.1 l/min ($P<0.05$).
Conclusions: Exercise capacity as assessed by oxygen consumption in patients with ASD is reduced. Significant improvement in exercise capacity occurred over the period of twelve months after transcatheter closure. These novel data emphazises the benefit of transcatheter closure as an alternative to surgery.

P3586 Transcatheter ASD closure with amplatzer device versus surgery in children-comparison of results and complications

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Objective: Comparisons of results, closure rates, morbidity and complications of transcatheter and surgical closure of ASDs in children performed at the same period and in the same institution.
Material & Methods: Our material comprised all children (2-18 y old) with ASDII and a pulmonary/systemic flow ratio of 1,5:1 or more admitted consecutively to Our Department between February 98 and November 00. All patients (pts) except those with defects unfeasible for interventional closure or children, whose parents prefered surgery were catheterized prior to planned transcatheter closure with Amplatzer Atrial Septal Occluder (ASO). Pts in whome catheter diagnosis proved that interventional closure was not possible underwent surgery. Complications after ASD closure were classified as mild, moderate and severe. Small pericardial effusion, headache and first degree av block were considered as mild - pneumonia, paroxysmal supraventricular tachycardia, nodal or atrial rhythm were described as moderate - bleeding requiring reoperation and transient neurological events were severe complications.
Results: 44 pts underwent surgery (S) at median age 8,1 (2,3-16,9) y and 47-ASO implantation at a median age 10 (2,3-17,7) y. No death occurred. Hospital stay in surgically treated pts was 10,5 (4-22)days versus 2,2 (1-15) days in ASO group ($p<0,001$). ASD size was larger in the surgical group ($p<0,001$). Closure rate was similar in both groups- S-95,5% vs ASO- 97,9%. Mild complications were observed in 17/44 (38,6%) of S group vs 2/47(4,3%) in ASO pts, moderate - 11/44 (25%) in S vs 1/47 (2,1%) in ASO pts and severe- in 2/44 (4,5%) of S group vs none in ASO group. Blood products were administered in 18 pts in S group and 1 in ASO group ($p<0,001$).
Conclusions: Trancatheter closure of ASDII with Amplatzer device has the advantage of fewer complications, shorter hospitalisation, reduced need of blood products and less patient discomfort. The surgeon's ability to close any ASD regardless of anatomy remains an important advantage of surgery. Complete closure rate is similar in both groups.

P3587 The application of interventional cardiac catheterization procedures as adjuncts to surgical management of single ventricle paediatric patients

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The aim of the study was a retrospective analysis of the types of cardiologic interventions employed in children with complex congenital heart defects (CCHD) and single ventricle (SV) depending on age, type and stage of surgical management. Material consisted of 70 patients (pts) with CCHD+SV treated 1.01.90-31.12.01. In course of hemodynamic diagnostic management these children were subjected to 72 interventions, what accounted for 22.2% of the total number of hemodynamic studies performed in CCHD+SVA pts. The pts were divided into 3 groups: 1)before hemi-Fontan (HF), 2)after HF, 3)after a modified Fontan (F) palliation. Results are presented in the table:

Stage	BAS/BFOD	Colis	BAA	BPA	Procedures	No patients
Before HF	16	2	15	0	32	30
After HF	0	28	4	6	38	38
After F	0	2	0	0	2	2

BAS/BFOD – ballon atrial septostomy/balloon foramen ovale dilatation,BAA – balloon aortic angioplasty, BPA – balloon pulmonary angioplasty,

Group 1: Among 30 children - BAS/BFOD was performed in 16 (53.3%) aged 0.56-5.5 mo,(x =2.2, SD=1.8), in 13 (43.3%) pts - 15 BAA was done when 3-7 mo (x = 5.5, SD=1.4), including 12 pts with aortic arch obstruction after Norwood procedure, and in 2 pts abnormal systemic to pulmonary collaterals were closed employing coils.
Group 2: Among 38 pts, in 28 (73.7%) major systemic-to-pulmonary collaterals were closed with coils at the mean age 47.5 mo (SD=36.9), and 3-108 mo (x=23.3,SD=23.2) after HF procedure, in another 6 pts (15.8%) BPA of left pulmonary artery was done when 12-30 mo(x=22.5, SD=7.2), 5-20 mo (x=13.1, SD=5.8) after HF, subsequent 4 (10.5%) pts (2 with HLHS and 2 with CCHD+SV and CoAo) underwent BAA when 18-24 mo(x=21.5, SD=2.6), i.e. x=13.8 mo,SD=2.4 after HF.
Group 3: In 2 pts at the age 13 and 11 yrs respectively closure with coils of systemic to pulmonary collateral in first and right to left interatrial communication in second was done.
Conclusions: In children before HF procedures the types of cardiologic interventions were associated with forms of congenital heart defects and types of previous operation. After the HF operation the most common procedure of coils embolization was associated with the development of abnormal systemic to pulmonary collaterals and not with the type of a defect or as initial surgery.

P3588 Balloon valvoplasty as an initial palliation in newborns with severely symptomatic tetralogy of Fallot

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Background: In newborns with tetralogy of Fallot (TOF), the pulmonary flow is limited by the stenosis or hypoplasia of the right ventricular outflow, pulmonary valve or pulmonary arteries. Balloon dilation of the critical stenosis may increase the pulmonary flow and prompt the growth of pulmonary arteries.
Method: From 1994 to 2001, percutaneous transluminal balloon valvoplasty (PTPV) was performed in 20 newborns and young infants with TOF. The indication for PTPV included severe hypoxemia (SpO2 below 75% under room air) and repeated hypoxic spells requiring intravenous propranolol or ambu-bagging or intubation. The age at PTPV ranged from 8 to 114 days (mean 38 ± 34 days, median 27 days) and the body weight was 3.45 ± 1.15 kg (median 3 kg). After the delineation of the right ventricular outflow and pulmonary arteries, a balloon catheter (4 to 6 mm in diameter and 2 cm in length) was used to dilate the pulmonary valve.
Results: No procedure-related complications occurred. The SpO2 increased significantly after the procedure (14 ± 9%). Thereby, a palliative shunt operation could be avoided in 8 patients (40%). Twelve patients still needed a palliative shunt operation (mean, 54 days after the PTPV) due to significant cyanosis or hypoxic spells. The presence of recurrent hypoxic spells before the dilation was the most important indicator of PTPV failure ($p=0.02$). Follow-up catheterization was performed in 14 patients and adequate pulmonary arterial size was found in all. Fifteen patients underwent total correction with one death.
Conclusion: PTPV could be safely performed in newborns and young infants with TOF to ameliorate the severe cyanosis and to prompt the growth of the pulmonary arteries. However, PTPV may be less effective to prevent the recurrence of hypoxic spells. Nonetheless, a palliative shunt operation may be avoided in about half of the patients. The advantages of prompted growth of the pulmonary arteries and the avoidance of a shunt operation and shunt-related pulmonary arterial distortion are addressed.

CARDIAC SURGERY – MISCELLANEOUS

P3589 Factors associated with cardiac complications during waiting for elective coronary artery bypass graft surgery

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Background: waiting lists for coronary artery bypass graft surgery (CABG) are inevitable in countries which depend on public health insurance. Severe and lethal cardiac events can occur during waiting for surgery.
Purpose: to identify factors associated with cardiac complications during waiting for elective CABG.
Patients and methods: four hundred ninety-three patients referred to elective CABG were separated into two groups: without and with cardiac complications during waiting for surgery, considered as worsening of functional class (FC, NYHA) to III or IV, unstable angina (UA), acute myocardial infarction (AMI), hospitalization or death due to cardiac causes. The groups were compared in regard to previous cardiac events, presence of risk factors, angiographic findings and results of non-invasive tests. Univariate analysis with chi-square and Student's t tests and logistic regression were performed.
Results: one hundred and eighteen (23.9%) patients had cardiac complication. Univariate analysis showed the following variables related to the presence of complication: female sex (OR 1.71, 95% CI 1.08-2.73, p=0.02), FC III or IV (OR 2.39, 95% CI 1.52-3.76, p<0.0001), previous UA (OR 2.24, 95% CI 1.25-4.02, p=0.005) and arterial hypertension (AH, OR 2.40, 95% CI 1.10-5.38, p=0.02). Waiting times were 148±148 and 179±161 days in the groups with and without complication, respectively (p=0.06). After logistic regression, FC III or IV, previous UA and AH were independently related to the presence of complication. Risk factors other than AH, previous AMI, coronary anatomy, left ventricular systolic function and ischemia at non-invasive tests were not significantly different between the groups.
Conclusion: FC III or IV at the moment of referral to CABG, previous UA and AH were associated with higher risk of cardiac complications during waiting for elective CABG. The findings must be considered when establishing priorities for the surgery, in order to minimize morbi-mortality during the waiting.

P3590 Predictors of mortality in patients with valvular heart disease waiting for cardiac surgery

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Background: A common feature of many Public Health Services is the existence of patients waiting for cardiac surgery. Previous studies have addressed this issue by establishing priority criteria for patients with coronary artery disease. However, there are scant data regarding patients with valvular heart disease.
Methods: The objective of the present study was to identify predictors of mortality in patients with valvular heart disease waiting for surgery. We have analysed 697 pts (age 65±11 years, 55% males) included consecutively in the waiting list, between January 1997 and May 2000, after an indication for isolated valvular surgery or combined valvular and coronary surgery.
Results: Mitral stenosis was present in 12% of patients, mitral insufficiency in 33%, aortic stenosis in 44% and aortic insufficiency in 20%. Significant coronary disease was detected in 20% of patients. The most frequent clinical presentation was heart failure (40%), followed by angina (19%) and syncope (5%). Only 7% of patients had a left ventricular ejection fraction <35%, and 32% showed pulmonary hypertension. Mitral surgery was performed in 33% of the patients, aortic surgery in 50% and combined mitral and aortic surgery in 13%. Associated coronary surgery was carried out in 20% of patients.
The delay before surgery lasted 132±129 days (range: 0-1.183 days). During this period 30 patients died (5%). Multivariate analysis (logistical regression) showed 4 independent predictors of mortality: 1) associated coronary disease (OR 1,77; CI 95% 1,14-2,76; p=0,01); 2) indication for mitral and aortic combined surgery (OR 2,15; CI 95% 1,37-3,37; p <0,01); 3) waiting time until surgery (OR 1,03; CI 95% 1,002-1,05; p= 0,02); and 4) severely depressed left ventricular ejection fraction (OR 4,15; CI 95% 1,30-13,1; p=0,01).
Conclusion: Thus, the reduction of waiting time until surgery and the prioritization of patients at high risk of death (associated coronary disease, mitral and aortic combined diseases, depressed ejection fraction) should decrease the mortality of patients with valvular heart disease while waiting for surgery.

P3591 Randomized study of the efficacy of oral diltiazem to prevent cardiac events after surgical revascularization with internal mammary artery

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Background: Calcium antagonists are widely used to prevent coronary spasm after coronary artery bypass grafting (CABG) with internal mammary artery (IMA) despite the lack of evidence of the proposed benefit.
Purpose: To determine the efficacy of oral diltiazem to prevent cardiac events in the first week after CABG with at least one IMA graft.
Methods: We randomly assigned 324 consecutive patients who underwent CABG with IMA graft to receive diltiazem retard 90 mg orally two times daily for 7 days, starting from arrival in intensive care unit (group A, 160 patients), or not to receive diltiazem (group B, 164 patients). Patients with emergency CABG, acute coronary syndromes and current therapy with calcium antagonists were not included in the study. Patients received all standard medications according to clinical condition, including beta-blockers. The two groups were matched for all preoperative characteristics, including age, sex, risk factors and preoperative left ventricular ejection fraction (EF). Primary end-points were episodes of coronary spasm and myocardial ischemia during 7 postoperative days. Secondary endpoints were myocardial infarction, cardiac death, arrhythmias, heart failure, and composite of total cardiovascular events.
Results: In the intention-to-treat analysis, no significant differences were found between the groups A and B in any of outcomes measured: coronary spasm (5/160 vs 3/164), myocardial ischemia (2/160 vs 5/164), cardiac death (1/160 vs 2/164), myocardial infarction (5/160 vs 12/164), arrhythmias (24/160 vs 18/164), heart failure (3/160 vs 2/164), composite of total cardiac events (40/160 vs 42/164). EF improved significantly postoperatively in both groups (from 48 to 49%, p=0.001, and from 48 to 49%, p=0.038, for groups A and B, respectively), although it was similar between groups A and B (50 vs 49%), as well as maximal postoperative serum creatine-kinase MB level (52 vs 60 IU).
Conclusion: It appears that oral diltiazem does not reduce the occurrence of coronary spasm and other cardiac events in the first week after CABG with IMA graft. Therefore, routine use of oral diltiazem in this setting should be discouraged.

P3592 Pharmacological strategies for myocardial protection in patients undergoing non-cardiac surgery: a meta-analysis of randomized controlled trials

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Introduction The impact of pharmacological interventions on the incidence of perioperative cardiac complications in non-cardiac surgery has not been systematically evaluated.
Methods A systematic search of full reports on randomized controlled trials on pharmacological myocardial protection in non-cardiac surgery was done. Dichotomous data was extracted on ischemia, non-fatal infarction, or cardiac mortality within 30 days after surgery. Meta-analyses were performed using a fixed effect model.
Results Beta-blockers (BB, six agents) were compared with placebo in 11 trials (877 patients), alpha2-agonists (AA, clonidine, mivazerol) in six (2,613 patients), calcium channel blockers (diltiazem, verapamil) in three (121 patients), and nitroglycerin in one (45 patients). There were no direct comparisons between different agents.
Ischemia: BB reduced ischemia intraoperatively (7.6% versus 20.2% with placebo, relative risk (RR) 0.40 {95%CI 0.24 to 0.67}) and postoperatively (15.2% vs 27.9%, RR 0.57 {0.37 to 0.87}). Patients on AA had less intraoperative ischaemia (19.4% vs 32.8%, RR 0.59 {0.46 to 0.76}).
Myocardial infarction: BB reduced the risk of infarction (0.9% vs 5.0%, RR 0.26 {0.11 to 0.63}) when two trials with high-risk patients were included. The effect of AA on infarction was not significant (6.1% vs 7.3%, RR 0.86 {0.65 to 1.14}). With both BB and AA there was a relationship between the pre-study prevalence of myocardial infarction, the incidence of infarction in controls, and the efficacy of these agents in preventing non-fatal infarction.
Mortality: Cardiac mortality was reduced with both BB (0.6% vs 3.1%, RR 0.39 {0.17 to 0.92} and AA (1.1% vs 2.3%, RR 0.53 {0.29 to 0.96}.
For calcium channel blockers and nitroglycerin, evidence of any benefit was lacking. With BB, the risk of bradycardia was significantly increased (24.5% vs 9.1%, RR 2.88 {1.96 to 4.23}).
Conclusions In patients at risk of cardiac complications undergoing non-cardiac surgery, beta-blockers and alpha2-agonists improve perioperative outcome

P3593 Endoventricular patch repair in postinfarction cardiomyopathy: comparison between early and late surgical experience

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Background: we started to perform endoventricular patch repair associated with CABG in 1985. Since then 1050 patients have been submitted to the procedure at the Cardiothoracic Center of Monaco. **Objectives:** to analyze if differences in surgical strategy and in clinical outcome existed between an old series of patients operated during 1991-93 and a more recent series operated between 1998-2000. **Patients and methods:** the first series (A) included 222 patients (60 ± 9 yrs; 33 F) and the second series (B) included 165 patients (63 ± 10 yrs; 29 F). All pts had associate coronary grafting; patch was used in 90% of pts in both series.
Results: in B operative mortality decreased from 8% to 5%, re-do surgery increased (9% vs 3%), a higher proportion of patients with recent myocardial infarction (MI) (≤ 3 months)was present. The reduction of volumes and the increase in EF was significant in both series. Surgical technical differences were the introduction of a balloon of known volume, to size the ventricle during reconstruction, and a more accurate peri-op assessment of mitral regurgitation (MR) with a consequent increase in mitral procedures, in B.The strategy to repair mitral valve in almost all patients with any grade MR and also in few patients without pre-op MR, but with annular dilatation, lead to a significant reduction in late MR in B. Mean pulmonary pressure increased significantly in patients whose mitral valve was not repaired (21±9 to 28±15 mmHg. P.0007)

Comparison between series (n° pts)

	Delay MI ≤3 m.	Pre-op MR	Patch	Mitral procedure	Mitral replace	Mitral repair	1 yr MR ≥2+
A	36/222	49/222	192/222	26/222	9/26	17/26	10/102
B	49/165	49/165	148/165	52/165	6/52	46/49	0/40
p value	0.0015	ns	ns	0.001	0.01	0.0001	0.037

MI: myocardial infarction; MR: mitral regurgitation.

Conclusions: the 2 most striking differences between the two series are 1) the decision to treat MR of any grade and to repair instead of replacing the valve; 2) the balloon-sized residual diastolic volume. This lead to a decreased operative mortality, to a lack of increase in pulmonary pressure and to a significant reduction of late MR, which is a critical issue in this procedure.

ATHEROSCLEROSIS AND CORONARY HEART DISEASE

P3594 Correlation between coronary calcium score and intima-media thickness at carotid arteries in patients with coronary artery disease

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There is scarce evidence on the relationship between coronary atherosclerosis and carotid thickening of intima-media, as well as between calcium score obtained in coronary arteries. The present study aimed to assess clinical application of coronary calcium score (CCS) and carotid intima-media thickness (IMT) measurement in patients with coronary artery disease (CAD).
Material and methods: One hundred patients, aged 59±9,4 years, admitted to the Department with suspected CAD were studied. Coronary Calcium Score (CCS), B-mode ultrasound quantification of carotid IMT and coronary angiography were obtained in all patients. CCS was measured using Multidetector Spiral CT (MSCT), Somatom Plus 4 Volume Zoom, software Calcium Scoring. CCS was calculated for left main, left anterior descending, circumflex and right coronary arteries. IMT was measured at left and right carotid arteries and expressed as the mean of the maximal value for the common carotid artery, bifurcation and the internal carotid artery. The statistical correlation between age and CCS, age and IMT, as well as between CCS and IMT were assessed by Pearson test. Furthermore, statistical analysis between advancing CAD and CCS, as well as advancing CAD and IMT were calculated using one-way variance analysis (ANOVA).
Results: Coronary angiography revealed 17 patients with no atherosclerotic lesions, 5 patients with non-significant atherosclerotic lesions, 30 patients with one-vessel CAD, 20 with two-vessel CAD, and 28 with three-vessel CAD. Statistically significant positive correlation between age and both CCS and mean IMT ($p<0,0000$ r= 0,486; $p<0,0001$ r= 0,385, respectively) was found. Greater mean IMT values were encountered in patients with two-and three-vessel CAD ($p=0,0530$ and $p=0,0009$), as compared to patients with normal coronary arteries. CCS values < 100 were detected in all patients with normal coronary arteries on angiograms. All patients with CS > 400 developed atherosclerotic lesions. Furthermore, 56% of patients with three–vessel coronary artery disease had CS > 400. Mean IMT correlated well with CCS ($p<0,0000$, r=0,506).
Conclusions: 1. The extent of calcification in coronary arteries and IMT of carotid arteries increases with age. 2. The increase of CCS and mean IMT are well correlated 3. CCS and mean IMT correlates significantly with advancing coronary artery disease.

P3595 Correlation of the severity of coronary atherosclerosis with extracoronary atherosclerosis

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Atherosclerosis is responsible for most cases of cardiovascular disease in the general population. Intima-media thickness (IMT) of common carotid and femoral artery is used as a marker of atherosclerotic changes of extracoronary arteries. The severity of coronary atherosclerosis can be described by Gensini score (GS). This study aimed to examine the relation between the extent of coronary and generalized atherosclerosis measures. Ninety one (33 - 72 years old, 29 female) patients referred for elective coronary angiography underwent ultrasound imaging for IMT measurement of carotid and femoral arteries. For further analysis we used separately the maximal and the minimal value of IMT measured for the right- and left-sided extracoronary arteries. The associations between Gensini score and IMT values were analyzed with the use of Spearman test with presentation of r coefficient and p value in the table below. There are significant and positive associations between GS and IMT values measured at the level of carotid and femoral arteries. The associations between IMT and GS are higher for carotid than for femoral arteries. The observed relationships are higher for the maximal than for minimal IMT values measured at the carotid level. Moreover, the highest observed associations are between GS and IMT values measured on the right-sided extracoronary arteries.

Correlation of GS with IMT

Extracoronary artery	Left-sided arteries	Right-sided arteries
Carotid - the maximal IMT	r=0.38; p=0.0002	r=0.46; p< 0.0001
Femoral - the maximal IMT	r=0.24; p=0.0225	r=0.34; p=0.0009
Carotid - the minimal IMT	r=0.19; ns	r=0.29; p=0.0054
Femoral - the minimal IMT	r=0.24; p=0.0197	r=0.36; p=0.0004

In conclusion, the indexes reflecting generalized and coronary atherosclerosis are significantly correlated. It seems that increased IMT of extracoronary artieries, particularly on the right side, may indicate the co-existence of coronary atherosclerosis.

P3596 Comparison of "average total thickness" of carotid arteries and stress/rest myocardial scintigraphy for the detection of coronary artery disease

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Background: An increase in intima-media thickness of the common carotid artery (IMT) has been confirmed as a surrogate marker for significant coronary artery disease (CAD). A mathematical model involving measurement of IMT and the areas of plaques in carotid beds may predict more accurately the atherosclerotic burden than IMT alone. One of these models the average total thickness of carotid arteries (ATT) was tested in our clinical trial.
Purpose: In this study we compared both parameters IMT and ATT respectively and results of stress/rest myocardial perfusion tomography performed with 99m-Tc-methylisobutyl-isonitrile (MIBI) for prediction of significant CAD.
Method: Carotid arteries were examined by ultrasound in consecutive patients referred to St. Paul's Hospital, Vancouver, Canada for MIBI test because of suspected significant CAD. Complete myocardial redistribution in rest and fixed myocardial perfusion defects were considered as positive MIBI test results. Values of IMT and ATT = 0,80 mm were considered cut-off points for significant CAD estimation.
Results: One hundred patients were eligible for the study (57 men and 43 women; average age, 60 ± 11 years). Positive MIBI test results were detected in 33 patients. Increased IMT was found in 38 patients and increased ATT was calculated in 73 patients. Accuracy both tests for prediction of positive MIBI test result is shown in the table (PV: predictive value).

Test	Sensitivity	Specificity	Positive PV	Negative PV	Odds ratio	P-value
IMT	0,52	0,69	0,45	0,74	2,33	0,05
ATT	0,88	0,34	0,40	0,85	3,79	0,02

Conclusion: According our results ATT value upon of 0,80 mm does not mean presence of myocardial perfusion defect. Lower value of ATT than 0,80 mm is significant negative predictive factor for myocardial perfusion defect. ATT calculation may thus reduce the number of patients undergoing stress/rest myocardial perfusion tomography.

P3597 Carotid lesion type is a marker of high risk coronary artery disease

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Objectives: to evaluate which carotid lesion characteristics predict high risk coronary anatomy in pts with known or suspected coronary artery disease (CAD). Methods: 162 consecutive pts, 116 males (71%), mean age 64± 10 underwent coronary angiography for known or suspected CAD and bilateral Eco-Doppler evaluation of carotid arteries by means of high resolution technique. Angiographic variables considered were number of critical (>70%) stenotic vessels by quantitative coronary assessment analysis and type of culprit lesions (A, B or C). Plaques were classified according to Gray Weale criteria (1-5). Plaques 2 and 3 were also classified as non-homogeneous.
Results: the average number of critical stenotic coronary vessels/pt was 1.4 (DS ± 1.1). In addition, 30, 20, 23, 27% of pts showed, 0, 1, 2 or 3 critical CAD, respectively. C coronary type lesions were present in 59% of the patients. At Echo-Doppler evaluation 32,6,12,27, 15, 8% of cases were characterized as 0, 1, 2, 3, 4 or 5 carotid type lesions, respectively. Carotid non-homogeneous type 3 lesions by Echo-Doppler were significantly correlated to presence of type C lesion at coronary angiography ($p < 0.001$). Conclusions: Presence of non-homogeneous plaques at carotid ultrasound scan is an index, in pts with known or suspected CAD, of the existence of high-risk plaques at coronary angiography.

P3598 Association of the increased carotid intima-media thickness with the severity of coronary artery disease

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Carotid intima-media thickness (IMT) is often used as a marker for coronary atherosclerosis. However, there is little evidence on the relationship between IMT and the advancing coronary artery disease. The present study aimed to investigate: 1) whether the increase in IMT is related to the severity of CAD, and 2) whether IMT might be instrumental in predicting patients with and without significant coronary atherosclerosis.
Methods: We examined 561 consecutive patients, (440 men, 121 women), aged 58,8 ± 9,2 years with suspected CAD. Coronary angiography, as well as ultrasound quantification of carotid artery IMT was performed in all patients. IMT was measured at both carotid arteries and expressed as the mean value, which was calculated for patients with normal coronary arteries, one-vessel CAD, two-vessel CAD and three-vessel CAD. A relation between IMT values and severity of CAD was determined by one-way variance analysis (ANOVA). Furthermore, nonparametric estimation of carotid mean IMT distributions was assessed with histograms using lognormal distribution in CAD patients and patients free of CAD. The positive and negative predictive values, as well as sensitivity and specificity were calculated to visualize the discriminating power of IMT. Results: On coronary angiography, 95 (16,9%) patients had normal coronary arteries. One-vessel CAD was diagnosed in 158 (28,2%) patients, two-vessel CAD in 100 (17,8%) patients and three-vessel CAD in 208 (37,1%) patients. In 90 patients a normal intima-media thickness (<1mm) was found, including 50 patients without atherosclerotic lesions on angiograms and 29 patients with one-vessel CAD. The mean measured value of IMT calculated for patients with normal coronary arteries was 1,01± 0,19 mm, with one-vessel CAD was 1,15 ± 0,20 mm, two-vessel CAD was 1,26± 0,27 mm, and three-vessel CAD 1,47 ± 0,34 mm. A statistically significant correlation between IMT and advancing CAD ($p<0.0000$ - ANOVA) was found. Notably, theoretical distributions of mean IMT revealed that patients with mean IMT value over 1,15 mm had 94% CAD probability, with sensitivity of 65% and specificity of 80%. We sought the cut-off points facilitating allocation of patients into one-, two- and three-vessel CAD. However, due to the overlapping distributions of IMT, this allocation procedure proved inadequate.
Conclusion: Ultrasound examination of carotid arteries can effectively predict atherosclerosis of coronary arteries. IMT increases with advancing CAD. Patients with mean IMT over 1,15 mm have high likelihood (94%) of CAD.

P3599 Changes in antibody titers against chlamydia pneumoniae after percutaneous transluminal coronary angioplasty

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Objective: We performed a prospective study in patients who underwent percutaneous transluminal coronary angioplasty (PTCA) to investigate whether angioplasty procedure would have an influence on the specific humoral immune response against Chlamydia pneumoniae (Cpn) antigens.
Methods and Results: Seventy six patients were included in the study. Blood samples were drawn immediately before PTCA and 1 month after PTCA. Specific IgG and IgA antibodies to Cpn were determined by enzyme immunoassay. At the time of angioplasty 75% and 34% of patients had seropositive antibodies to EBs of classes IgG and IgA respectively. Mean titers of IgG antibodies before and one month after PTCA were 46±31 RU/ml and 50±28 RU/ml ($p>0.05$). One month after PTCA, 98% and %34 of the patients had seropositive antibodies to EBs of classes IgG and IgA respectively. We divided patients into two groups on the basis of IgG seropositivity (Group I: Cpn antibody IgG seronegative, group II: Cpn antibody IgG seropositive) before PTCA. Significant increase in antibody titers of IgG(12±5 RU/ml vs 40 ±18 RU/ml $p<0.001$) and IgA (0.6±0.33 RE/ml vs1.15±0.83 RE/ml $p=0.007$) was observed in group I patients one month after PTCA and 88% of them gained IgG seropositivity. There were not siginificant changes of IgG and IgA antibody levels in group II after PTCA.
Conclusion: We have showed a statistically significant rise in Cpn specific antibodies especially of IgG induced by PTCA in seronegative patients before PTCA. This finding highlights the difficulties of relying on serological diagnosis of infection in coronary artery disease.

P3600 Association between PET flow capacity and inflammation assessed from VCAM-1 and minimal coronary resistance at early coronary atherosclerosis

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Coronary atherosclerosis is an inflammatory disease and endothelial vascular adhesion molecule (VCAM-1) exerts a pivotal role at early atherogenesis. Purpose of our study was to relate soluble VCAM-1 levels to myocardial blood flow (MBF) response in 20 patients with mild-to-moderate LDL hypercholesterolemia, mild angina pectoris (CCS class I-II or atypical angina), reduced coronary vasodilator capacity on dipyridamole (D) PET at baseline and minimal coronary disease on angiography (CAD) before and after 5-6 months of intensive lipid-lowering (fat-reduced diet combined with statin therapy), previously not receiving lipid-lowering drugs. Exclusion criteria were smoking, diabetes, hormonal replacement, significant LV hypertrophy and cardiomyopathies.
Methods: VCAM-1 was measured by ELISA technique. 15 apparently healthy age-matched (51-60 years) blood donors (10 males) served as controls: VCAM-1: 810± 243 ng/mL. For quantitative analysis with PET (Siemens ECAT 9.51) a 3-compartment model for MBF (~ 550 MBq N-13 ammonia) determination was applied. Pts had reduced mean global flow reserve (2.2±0.6) versus controls (4.0±1.3, $p<0.01$) on D-PET (0,56 mg D/kg). Dilator capacity was noninvasively assessed as minimal coronary resistance (MCR) normalizing D-MBF on mean perfusion pressure.
Results: Baseline data (mean ± SD): age 58±9, (14 males); VCAM-1 at baseline 1215±368 ng/mL, total cholesterol 244 ±43, HDL-C: 47±19 mg/dL. VCAM-1 decreased from 1215±368 to 850 ± 343 ($p<0.01$) and MCR from 0.495±0.09 to 0.37±0.10 mmHg/mL/min x 100 g ($p<0.01$). A positive correlation was obtained between VCAM-1 (x) and MCR (0.372+6.128 E-5x).
Conclusions: Lipid-lowering guided by statins and PET exerts a beneficial short-term effect on inflammation in terms of VCAM-1. Our data suggest an important relation between impairment of coronary dilator capacity, determined noninvasively by PET, and a molecular marker of inflammation, demonstrated to the best of our knowledge for the first time at early CAD with near normalization of MCR after statin therapy.

P3601 Cardiovascular risk factors profile and the risk of developing acute coronary syndromes, in Greece: final results from CARDIO2000 study

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Background: During the past decades several epidemiological studies have provided a portrait of the potential candidate for cardiovascular disease. Additionally, many differences arose in the coronary risk models, between populations as well as among individuals within populations that made extremely difficult the generalization of the results. The aim of this study is to model the coronary risk, based on several established and emerging risk factors, in a Mediterranean population and to compare the findings with other similar studies.
Methods: During 2000-2001 Athens Medical School and Hellenic Heart Foundation conducted a multicentre (35 coordinators from all regions) epidemiological study. 701 males and 147 females patients with first event of an acute coronary syndrome and 1078 matched by sex, age and region, controls, randomly selected from the daily listings of the cardiology clinics and completed a detailed questionnaire concerning more than 100 parameters. Conditional logistic regression analysis estimated the relative risks of developing coronary heart disease under several hypotheses and stage II meta-analysis compared our findings with other major epidemiological studies (The Seven Countries Study, The Framingham Heart Study).
Results: Mean age for first event in the series of male patients was 58±10 and for the females, 65±9 years old. The frequency ratio between males – females was 4-to-1. The hierarchical regression analysis showed that: sedentary life (OR=1.98, P-value < 0.001), hypercholesterolemia (OR=5.25, P-value < 0.001), adoption of Mediterranean diet (OR=0.90, P-value < 0.001), depression (OR=1.05, P-value < 0.01), hypertension (OR=2.79, P-value < 0.05), smoking (OR=2.27, P-value < 0.05), diabetes mellitus (OR=2.67, P-value < 0.05), family history (OR=2.47, P-value < 0.05), job stress (OR=2.23, P-value < 0.05), and educational level (OR=0.63, P-value < 0.05) were independently related with the risk of developing the disease. By the application of (stage II) meta-analysis we found many differences as well as many similarities (P-value < 0.01) with the stochastic models based on different populations.
Conclusion: With respect to any potential, systematic error we conclude that several emerging lifestyle risk factors in addition to the conventional, pose their particular challenge for further research, in this Mediterranean population. Moreover, the applied meta-analysis supported the hypothesis for heterogeneity of risk charts between populations and, consequently, the need for local epidemiological studies (Pyorala K. Eur Heart J, 2000).

P3602 Heavy metals ions seem to have no significant effect on extent of coronary artery disease

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There are still unsolved issues concerning the role of heavy metals ions (HMI) in pathogenesis and progression of atherosclerosis. Some of them like selenium (Se) and zinc (Zn) are thought to have positive effect on endothelium, others like lead (Pb), cadmium (Cd), manganese (Mn) and copper (Cu) can probably deteriorate its function. The link between HMI and extent of macroscopic atherosclerosis is unclear.
The aim of study was to find out the relation between blood and plasma concentration of HMI and extent of atherosclerosis in coronary arteries in patients (pts) with coronary artery disease (CAD).
Study population consisted of 60 pts (32 men and 28 women) mean age 62,4 ± 10,5 yrs, all former or current smokers with no history of working in environment with high exposure to HMI. The diagnosis of coronary artery disease was established upon coronary angiography in which 70% narrowing of the vessel was considered as significant. Pts were divided in to four groups according to the number of affected arteries (0, 1, 2, 3). Blood concentrations of Cd and Pb and plasma concentrations of Cu, Zn, Mn, Se were estimated by SAA method (Spectrophotometry Atomic Absorption).
Results are shown in the table.

Coronary artery disease extent groups	Zn (μg/dl)	Mn (μg/l)	Cu (μg/dl)	Cd (μg/l)	Se (μg/l)	Pb (μg/l)
0 (n=19)	97,63	1,27	108,96	0,31	58,41	40,15
1 (n=18)	93,09	1,10	119,00	0,09	67,47	39,88
2 (n=11)	104,37	1,52	122,11	0,27	63,75	46,51
3 (n=12)	98,57	1,41	115,75	0,38	57,62	47,10
Statisticaly significant differences	NS	NS	NS	NS	NS	NS

Blood concentrations of Cd and Pb were below threshold limit value for non-exposed population and plasma concentrations of Zn, Mn, Se, Cu were within normal limits. No significant differences in concentrations of HMI among studied groups were found out.

Conclusion: In conclusion we can state that in patients with CAD: 1. Blood concentrations of Cd and Pb and plasma concentration of Zn, Mn, Se and Cu do not differ from those in normal population. 2. There is no relation between blood and plasma concentrations of studied HMI and extent of atherosclerosis in coronary arteries.

P3603 Correlation between extent of coronary calcification and predicted cardiovascular risk based on risk factor models in primary prevention

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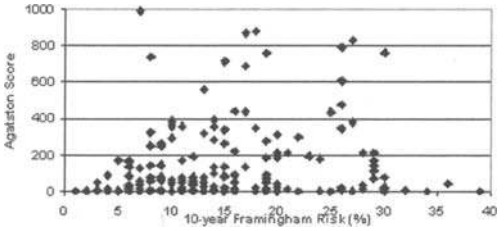
We investigated the relationship between the extent of coronary calcifications (CC) quantified by electron beam tomography (EBT) and the predicted 10-year cardiovascular event risk based on Framingham and PROCAM data in primary prevention patients in order to verify whether EBT information is independent from and additive to that obtained by traditional risk factor analysis.
Methods: In 250 subjects (180 men, 70 women, mean age: 58 years), CC were quantified by EBT using the "Agatston Score" (AS). The predicted 10-year cardiovascular event risk was determined using the Framingham equation (FRA) and (in men) the PROCAM algorithm.
Results: In 186 subjects, CC was detected by EBT. Mean AS in all patients was 194. The mean FRA risk was 10.9% in patients without CC and 15.4% in patients with CC (p = 0.001). The mean PROCAM risk in men without CC was 5.4% vs. 7.9% in men with CC (p = 0.09). 49 subjects had a FRA risk > 20%, ("high-risk patients"). 8 of these had an AS of 0, which implies a very low cardiac risk. 2 of 97 patients with a FRA risk below 10% ("low risk") had an AS exceeding 400, which in turn implies a very high cardiac event risk. Only 30 of 62 subjects in the upper quartile of FRA risk (>19%) were in the upper AS quartile (AS > 171). The graph shows the correlation between FRA risk and AS (r^2=0.06).



"Agatston Score" vs. Framingham risk.

Conclusions: The presence and quantity of coronary calcifications shows no close relationship to the extent of traditional risk factors. Particularly, a substantial fraction of patients with high risk according to risk factor based prediction models have no coronary calcifications and thus may be at lower risk. The assessment of coronary calcium therefore yields independent and additional information to prediction models based on traditional risk factors.

P3604 Plasminogen levels and risk of coronary artery disease – A case-control study

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Background: The plasminogen system has strong fibrinolytic and proteolytic properties and plays an important role in inflammatory and other cell migratory processes. Experimental studies suggest an importance of plasminogen-mediated proteolytic degradation of extracellular matrices in tissue remodeling events like atherosclerosis and restenosis. The aim of this case-control study was to investigate the association of systemic plasminogen levels and the presence of chronic coronary heart disease (CHD).
Methods: Cases included 312 clinically stable patients with CHD aged 40-68 years who underwent coronary angiography and who had at least 1 coronary stenosis >50%. Age- and sex-matched voluntary blood donors served as controls (N=479). Plasminogen activity was measured in double in citrate plasma by chromogenic assay (Chromogenix, Milano, Italy). Further sensitive markers of fibrinolysis, hemostasis and inflammation were determined.
Results: Plasminogen levels were not statistically significant different between patients with CHD (113.6% activity) and healthy controls (114.1% activity). Plasminogen levels were positively correlated with fibrinogen ($r=0.26$, $p<0.0001$), plasma viscosity ($r=0.34$, $p<0.0001$), serum amyloid A ($r=0.16$, $p<0.001$), C-reactive protein ($r=0.12$, $p<0.01$), apolipoprotein A1 ($r=0.16$, $p<0.001$), apolipoprotein A2 ($r=0.14$, $p<0.01$), and total cholesterol ($r=0.17$, $p<0.001$). After multivariable adjustment for age, sex, body mass index, smoking behavior, alcohol intake, years of school education, HDL-cholesterol, history of hypertension and diabetes, the odds ratio of stable CHD for elevated plasminogen levels (highest versus lowest quartile) was 0.8 (0.5-1.3).
Conclusion: Levels of plasminogen are not associated with the presence of CHD in this study population. Thus, measuring systemic plasminogen activity has no additionally benefit in predicting CHD at least in patients with stable angina.

SMOKING AND ITS EFFECTS ON THE CARDIOVASCULAR SYSTEM

P3605 Acute passive smoking induces oxidation of low-density lipoproteins and impairs endothelium dependent arterial dilatation

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Background: Passive smoking impairs endothelial function and is one of the major risk factors for atherosclerosis and coronary heart disease. The aim of the present study was to examine whether acute passive smoking (1) accelerates lipid peroxidation; (2) causes acute endothelial dysfunction, in nonsmoking healthy young men.
Methods: Study subjects were consisited of 14 healthy nonsmoking young men without history of hypertension, diabetes mellitus, or hyperlipidemia. Before and after a 30-minute exposure to environmental tobacco smoke, we measured the serum levels of malondialdehyde-modified low density lipoproteins (MDA-LDL) as an index of lipid peroxidation, and assessed flow mediated vasodilation (FMD) in the brachial artery using high resolution ultrasound (7.5 MHz) at baseline and during reactive hyperemia.
Results: Passive smoking acutely (1) increased the serum levels of MDA-LDL (98 ± 17 to 118 ± 18 U/L, $P < 0.05$); (2) impaired the FMD (11.6 ± 4.7 to $5.3 \pm 3.8\%$, $P < 0.01$).
Conclusions: Acute passive smoking substantially (1) induced lipid peroxidation assessed by the increased serum levels of MDA-LDL; (2) impaired endothelium-dependent vasodilation in the brachial arteries. The precise mechanisms by which acutely increased MDA-LDL causes this altered vascular reactivity remain unclear, however, these findings provide a clinical evidence that even an acute passive smoking may be dangerous.

P3606 Cigarette smokers and vascular damage: analysis of mechanisms that impair endothelium dependent vasodilatation

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Background: Cigarette smokers have an impaired endothelium dependent vasodilatation (EDVD). The precise mechanism of smoking related endothelial dysfunction is unknown, and may be multifactorial. An abnormal EDVD may be caused by decreased nitric oxide (NO) production or by increased NO inactivation due to the action of free radicals, or both.
Methods: To investigate this question, we enrolled 52 patients [age 48.5 ± 10.5 years (range: from 35 to 64); 53.8% males (n = 28)]: 25 of these (48% of the study population) chronic smokers and 27 (52%) control not-smoking subjects. Patients were studied after an overnight fasting period; an ultrasonographic study of the brachial artery was performed and a urine sample was collected for each patient. EDVD was evaluated by measuring the diameter of the brachial artery before and during reactive hyperaemia (induced after deflation of a blood pressure cuff inflated to suprasystolic pressure for 5 minutes) and was calculated from the diameters as: (reactive hyperemia - baseline)/baseline X 100%. Urine levels of Isoprostane 15-F2t-isoprostane (IsoP) (a stable metabolite of arachidonic acid) was dosed to represent an index of free radical production. Urinary escretion of nitrates was measured as the product of whole-body NO synthesis.
Results: (Data are expressed as mean value ± SEM). Greater EDVD resulted in the non-smoker group than in the group of cigarette smokers (6.3 ± 0.3 versus 2.6 ± 0.3; $p < 0.001$). Additionally we noticed higher urinary levels of IsoP in smokers (14.2 ± 3.8 versus 4.94 ± 2.7 ng/mg creatinine; $p < 0.05$). There was a significant inverse correlation between EDVD and urinary levels of IsoP in smokers ($r = -0.72$; $p < 0.0001$). Nitrate urine levels were similar in the two groups (765.6 ± 157.0 in smokers versus 647.1 ± 136.4 mmol nitrate/mg creatinine in the other group; p = ns).
Conclusions: Smoking is not accompanied by less total production of NO; abnormal EDVD is associated with enhanced oxidative stress due to overproduction of free radicals.

P3607 Acute cigarette smoking and endothelium. Effect of regular versus "light" cigarettes

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Acute cigarette smoking leads to temporary endothelial dysfunction. To examine the effect of regular versus "light" cigarettes on endothelium, 11 healthy individuals (6 women, 5 men, age 27.2±3.7 years) underwent measurement of endothelial function of the brachial artery (endothelium-dependent, flow-mediated dilatation, FMD). Measurements were performed before, immediately after and 30, 60 and 90 minutes after smoking one cigarette. Subjects were randomized to smoke either a regular cigarette (nicotine 0.9 mg, tar 12 mg) or the corresponding "light" cigarette (nicotine 0.6 mg, tar 8 mg). The following day, measurements were repeated after smoking the opposite kind of cigarette. Results: In the group of regular smoking FMD was 7.5±2.6% and was reduced to 1.7±3.8% immediately after smoking, 1.3±2.7% at 30 min, 5.0±3.0% at 60 min and 5.8±2.3% at 90 min. FMD reduction was significant immediately after smoking and at 30 min ($p=0.016$ and $p<0.001$ respectively). In the group of "light" smoking FMD was 6.1±1.7% and was reduced to 2.9±2.5% immediately after smoking, 4.4±3.8% at 30 min, 5.7±2.7% at 60 min and 6.5±2.8% at 90 min. FMD reduction was significant only immediately after smoking ($p=0.008$). FMD comparison between the two groups showed no difference before and immediately after smoking (ns), statistically significant difference at 30 min ($p=0.023$) and no difference at 60 and 90 min (ns). In conclusion, both regular and "light" cigarette acute smoking lead to endothelial dysfunction; the duration of endothelial dysfunction after acute smoking is shorter with "light" cigarette smoking.

P3608 Smoking a cigarette while drinking coffee: how badly is aortic function affected?

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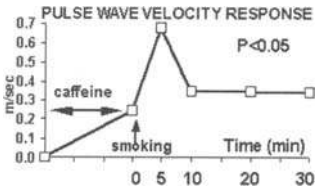
Background: Aortic stiffness is an important determinant of left ventricular function and coronary blood flow and has been identified as a prognosticator of cardiovascular risk. We have previously shown that caffeine increases aortic stiffness. The habitual consumption of caffeine is often associated with smoking; however, their combined effect on aortic stiffness has not been defined.
Methods: We studied 10 healthy volunteers (age 30±5 years) in a randomized, placebo-controlled, crossover fashion (200 mg of caffeine orally -equivalent to 1-2 cups of coffee- and 60 min later smoking one standard cigarette -1.1 mg nicotine- or placebo and sham smoking). Carotid-femoral pulse wave velocity was measured as an index of aortic stiffness. Pulse wave velocity (=dL/dt, where dL is the distance travelled by the pulse and dt the time delay between the corresponding foot of pulse waves) was measured using an automated, non-invasive device (Complior®) that has been previously validated.
Results: Caffeine led to a substantial increase in pulse wave velocity (by 0.24 m/sec) that denotes increase in aortic stiffness. Smoking increased further pulse wave velocity (by 0.44 m/sec, figure). Pressures also increased (systolic: by 16.8 with caffeine and by an additional 7.5 mmHg with smoking; diastolic: by 10.8 with caffeine and by an additional 5.1 mmHg with smoking).



Smoking/coffee and aortic stiffness.

Conclusions: Smoking and caffeine have a synergistic adverse effect on aortic stiffness. This finding has important implications for left ventricular function and coronary blood flow and provides a new insight into the combined effects of smoking and caffeine on the cardiovascular system.

P3609 Immediate effect of cigarette smoking on the QT-interval in habitual smokers

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Introduction: Conflicting results are available on the impact of smoking on ventricular repolarization, and the immediate effect of smoking on the QT interval has not been adequately studied yet. The aim of the present controlled study was to assess the effect of smoking on the QT interval duration in healthy smokers after an overnight cessation of smoking.
Methods: 19 healthy volunteers (32±13, range 18-58 years, 8 men) were enrolled. All patients had normal baseline ECGs. On the first day subjects simulated smoking with tobacco void cigarettes (sham-smoking). On the other day, subjects were asked to smoke 4 cm of a filter cigarette containing 0.9 mg of nicotine in 2 minutes. Carboxyhemoglobin levels were determined before the experiments to rule out prior smoking. Twelve-lead ECG-s were recorded in every 2 minutes, QT interval was measured in five consecutive cycles in lead II using a digitising board and computer. Bazett's square root, Fridericia's cubic root formulas and the linear equation of Sagie (QTLc = QT+0.154[1-RR]) were used to adjust the QT interval for heart rate.
Results: Smoking induced a statistically significant immediate increase in heart rate, whereas sham smoking had no significant effect on heart rate. After smoking QTc significantly increased, but neither smoking nor sham smoking influenced QTFc and QTLc values.

Table

Difference (post - pre)	Sham smoking	Smoking	P
HR (bpm)	-0,1±2,3	19,0±12,2	<0,001
QTc (ms)	-6,8±7,5	12,7±3,9	<0,0001
QTFc (ms)	-6,5±6,7	-3,7±9,0	NS
QTLc (ms)	-6,2±6,7	-4,4±9,0	NS

Conclusion: 1) Smoking seems to have no immediate effect on the corrected QT interval. 2) Our data indicate that the increase of QTc after smoking results from the higher heart rate, because QT values corrected with more accurate formulas remained unchanged. 3) We suggest that the application of the Bazett formula should be avoided when comparing groups for QT interval duration with different baseline heart rates.

P3610 Age related differences in variables associated with smoking habit in adolescence

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Background Adolescents cigarette smoking is related to several factors. However limited information exists about the differential role that these factors may play at different ages. In this study we investigated which factors were associated with smoking habit in two age group (14-16 and 17-19 years) high school students.
Methods The smoking habit of 904 students (506 males, 398 females) attending a high school located in Naples, Italy, was evaluated by an anonymous, self-administered questionnaire including questions on student, parents, sibling(s) and peer smoking habit, student alcohol and illicit drug use and attitude towards smoking.
Results The smoking habit was as common in girls as in boys and increased with age. In the group as a whole and in the two age groups, smoking habit was related to number of hours spent with friends of opposite sex (p=.004), age of first puff (p<.001), positive attitude towards smoking (p=.002), smoking in home with parents (p=.024) and illicit drug use (p=.004). In the younger age group other factors related to smoking were: money avalaibility (p=.041), have smoked a cigar (p<.001), percent of friends who try to smoke (p=.060), number of days in which the student drank (p<.001), have drunk beer in the last month (p=.001) and get drunk at least once (p=.057). In the older age group other factors associated with smoking were: intention to leave the school (p=.055), have a sibling who smoke (p=.004), smoking habit of best friend of same sex (p=.032) and have drunk spirit in the last month (p=.006).
Conclusions: Adolescents smoking habit is associated with several age-related factors. Those factors specifically related to smoking in younger students witness their intention to seem "adult" whereas, in older students, the distinctive factors related to smoking are expression of the process aimed to construct an own self-identity. This observation might have relevant preventive implications.

P3611 Smoking and inflammatory indices – Dependent or Independent risk factors for coronary artery disease

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Background: Smoking-induced endothelial dysfunction may lead to cytokine- and adhesion molecule-mediated inflammatory activation within a vascular wall.
The aim of the study was to assess the relationship between the smoking status and serum levels of TNF (Tumor Necrosis Factor)alpha, sTNFR (soluble form of TNF receptor) 1 and 2, and selected adhesion molecules (AM): E-selectin, P-selectin, VCAM-1 (Vascular Cell AM-1) and ICAM-1 (Intercellular AM-1) in patients (pts) with coronary artery disease (CAD).
Methods and Results: The study group consisted of 101 consecutive admissions with stable CAD (class II/III CCS; age: 58.9±9): 27 current smokers (group 1; age: 53.6±9), 30 ex-smokers (group 2; age 56.1±7) and 44 pts who have never smoked (group 3; age: 62.8±8). 20 healthy volunteers were the controls (group C; age: 55.3±6). Serum TNFalpha levels were higher in pts with CAD (1: 17.8±2 pg/ml; 2: 16.5±3pg/ml; 3: 17.7±5 pg/ml; p<0.001) than in healthy subjects (8.3±1.4pg/ml). Mean serum concentrations of sTNFR 1 were significantly higher in group 3 (1595±660 pg/ml; p<0.05) in comparison both to group 1 (1306±433 pg/ml) and the controls (1094±457 pg/ml). AM determinations revealed the following: elevated serum E-selectin in all patient groups as compared to group C - with the highest concentrations found in group 1; VCAM-1 elevation in groups 1 and 2 as compared to the controls. P-selectin levels were increased in CAD pts regardless of their smoking status. There were no differences between ICAM-1 levels in the groups examined.
Conclusions: Serum concentrations of some cytokines and adhesion molecules are increased in pts with CAD. Cigarette smoking influences the E-selectin and VCAM-1 serum levels. CAD pts who have never smoked are characterized by delayed onset of angina that might be partly related to the elevation of sTNFR 1 concentration.

P3612 Documentation of slow coronary flow by the TIMI frame count in habitual smokers with normal coronary arteries

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Background: It is well known that cigarette smoking impairs the endothelial function, alters the neurohumoral and autonomic regulation. It has been suggested that in healthy subjects, the long-term effects of smoking is related to abnormal coronary vasomotion, presumably induced by an interplay of regional endothelial dysfunction and autonomic dysregulation. Thrombolysis in Myocardial Infarction (TIMI) frame count is a simple clinical tool for assessing quantitative indexes of coronary blood flow. In this study we aimed to evaluate the effects of long-term cigarette smoking in patients with angiographically proven normal coronary arteries.
Methods: Between May 2001 and January 2002, 41 habitual smokers and 41 sex-matched nonsmokers with angiographically proven normal coronary arteries were included in the study. Patients were divided into two groups; group I consisted of 41 patients; 29 men, 12 women mean age=46, range from 39 to 62)who were heavy habitual cigarette smokers, as determined by the high Fagestrom scale. Nonsmokers (group II, mean age=49 range from 42 to 66) were defined as who had never smoked a single cigarette, cigar or pipe.
Results: Resting heart rate was significantly increased in smokers compared with nonsmokers (76±6 vs 71±7 beats/min, $p<0.05$). TIMI frame count of the smoking group was significantly higher than those of nonsmokers for all three coronary arteries: left anterior descending (corrected TIMI frame count), 39±13 vs 22±8 respectively, right coronary artery, 35±13 vs 24±11 respectively left circumflex artery, 37±13 vs 25±8 respectively ($p<0.001$ for all). The smoker patients were tended to be younger than nonsmoker patients (46±7 years vs 49±9 years respectively p=0.07).
Conclusion: We have shown that TIMI frame count is significantly increased in habitual smokers with angiographically proven normal coronary arteries when compared with nonsmokers. Increased TIMI frame count in smokers can be regarded as the index of harmful effects of smoking on coronary flow regardless of the underlying mechanisms.

P3613 Characteristics of coronary patients who smoke

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Background: Smoking increases the risk of coronary atherosclerosis (CA). Therefore, the characteristics of coronary patients who smoke are of particular interest.
Materials and Methods: We investigated 767 consecutive patients undergoing coronary angiography. Of these patients, 156 were current smokers and 319 had never smoked. Comparisons were made between these 2 groups. The remaining patients had quit smoking and are not reported here.
Results: Among smokers the prevalence of CA was higher (83 vs. 73%; p=0.016), and there were more men (81 vs. 44%; $p<0.001$), more patients with diabetes (28 vs. 19%; p=0.037), and fewer patients with a family history of atherosclerotic disease (41 vs. 58%; p=0.001). In this group, mean age was lower (55 vs. 66 years; $p<0.001$), body mass index (27.9 vs. 26.6 kg/m^2; p=0.003), waist/hip ratio (0.97 vs. 0.91; $p<0.001$), and alcohol consumption (11.7 vs. 3.9 g/day; $p<0.001$) were higher; HDL cholesterol (44 vs. 53 mg/dl; $p<0.001$) was lower, and apolipoprotein B (120 vs. 112 mg/dl; p=0.002) was higher, whereas LDL cholesterol was unchanged (133 mg/dl in both). Fasting plasma glucose (119 vs. 112 mg/dl; p=0.037), CRP (10.8 vs. 8.2 mg/dl; $p<0.001$), fibrinogen (366 vs. 339 mg/dl; p=0.004) and leukocyte count (8.9 vs. 6.8 G/dl; $p<0.001$) were increased in smokers. Moreover, in smokers the severity (average percentage of all coronary stenoses), but not the extent (number of coronary stenoses) of CA was increased (p=0.002).
Conclusions: In coronary patients smoking is associated with a large scale of cardiovascular risk factors. Morphologically, the severity rather than the extent of CA is increased by smoking.

P3614 Association of smoking with markers of systemic inflammation: results of a population-based study

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Smoking is capable of inducing a low-grade inflammatory response and inflammation in the arterial wall plays an important role in atherosclerosis. We sought to investigate the association between various markers of systemic inflammation and a detailed history of smoking in a large representative sample of the general population.
We measured the effects of chronic smoking on white blood cell (WBC) count, fibrinogen (FIB) and albumin (ALB), plasma viscosity (PV), and high-sensitivity C-reactive protein (CRP) in 2285 men and 2201 women, age 25-74 years, participating in the third MONICA Augsburg survey 1994/95.
Current smokers showed statistically significantly higher values for WBC count, FIB, PV, and CRP, compared to never smokers (all $p<0.001$), with intermediate, but only slightly increased values for ex-smokers and for occasional smokers. No associations were seen with ALB. Duration of smoking was positively correlated with markers of inflammation as were pack-years of smoked cigarettes. Conversely, duration of abstention from smoking was inversely related to these markers. Adjustment for multiple covariates did not appreciably alter these associations. No clear relationship was found between markers of inflammation and indicators of passive smoking.
Data from this large representative population thus show strong associations between smoking and various markers of systemic inflammation in both sexes and various age groups. They also show that cessation of smoking decreases the inflammatory response, which may represent one mechanism responsible for the reduced cardiovascular risk in these subjects.

PRIMARY PREVENTION

P3615 Prevention of contrast media-induced renal failure after coronary angiography – First results of the "Diuresis versus Dialysis (DVD) study"

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Different stragies for prevention of contrast media induced acute renal failure (ARF) have been investigated demonstrating the importance of hydration with hypotonic infusions (2x1000 ml 0.9% NaCl + 5% glucose, Solomon, N Engl J Med 1994) as well as a significant reduction of ARF by administration of 2x600 mg n-acetylcystein (NAC) over 2 days (Tepel, N Engl J Med 2000).
In a prospective randomized trial with patients (NYHA I-II) undergoing elective coronary angiography with the non-ionic contrast dye iopromide, we included until now 136 patients with moderate chronic renal failure (creatinine 1.3-3.5 mg/dl) and randomized them to one of the following treatments: hydration alone (n=46), hydration + NAC (n=38), and hydration + onetime hemodialysis (n=45). Target is the inclusion of 402 patients, with a statistical power to detect a 25% difference of one of the treatments. Clinical endpoint is ARF (defined as an increase in enzymatically determined creatinine of 0.5 mg/dl). Further, laboratory parameters were monitored as serum creatinine levels, measurement of creatinine clearences, microalbuminurie, and cystatin at baseline, 24 h, 48 h, and 1 month after angiography. Between the three groups, there were no differences in age, gender, frequency of risk factors as hypertension, or dyslipoproteinemia. Average amount of contrast media was 190±11 ml in each group. The most important parameters at baseline and after contrast media exposition are shown in the table, with no significant differences. Frequency of diabetes ranged from 25.7 to 31.3% in the groups. Of the 11 patients with ARF, 7 were diabetics (64%). Hydration alone showed a higher rate of ARF (30%) in diabetic patients compared to addition of NAC or dialysis (each 15%, n.s.).

Patient's characteristics

	Hydration	Hydration+NAC	Hydration+dialysis
Baseline crea, mg/dl	1.46±0.22	1.68±0.47	1.51±0.26
Increase in crea, mg/dl	0.10±0.21	0.21±0.34	0.13±0.15
Filtration rate, ml/min	90.5±48.4	72.4±37.3	77.6±43.5
Decrease in filtration, ml/min	11.8± 36.2	19.8±27.2	16.5±28.2
Patients with ARF, n (%)	4 (8.2%)	4 (9.8%)	3 (6.5%)

At this time, no significant difference in frequency of ARF after coronary angiography between the different treatment groups could be found.

P3616 The combined family history risk score: a prognostic risk factor of acute coronary syndromes. The CARDIO2000 Study

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Background: Although the family history of premature coronary heart disease (CHD) is considered a significant risk factor in the development of acute coronary syndromes (ACS), data regarding the importance of the other risk factors that aggregate in families are sparse in the literature. In this work we present a risk score for developing ACS based on family history of hypertension, hypercholesterolemia, obesity, diabetes mellitus, premature CHD and family smoking habits.
Methods: The studied population consisted of 848 randomly selected patients with first event of ACS and 1078 matched, by sex-age-region controls admitted to the same hospitals for minor operations and without any suspicion of cardiovascular disease in their life. The investigation of family history score in the development of ACS was based on Fisher's discriminant function and on conditional logistic regression (odds ratio; 95% confidence interval), controlling for demographic variables as well as for the mutual confounding effects of the other risk factors.
Results: The introduced combined family risk score was positively related with the risk of developing ACS (P for trend < 0.001). In particular, the additive risk model showed that family history of CHD increases by 33% the individuals' coronary risk (OR=1.33; 1.21-1.78). In addition, presence of hypercholesterolemia, within the family, increases the previous risk by 39% (OR=1.39; 1.23-1.88); hypertension by 45% (OR=1.45; 1.23-2.12); diabetes mellitus by 78% (OR=1.78; 1.38-2.23); obesity by 97% (OR=1.97; 1.43-2.52); and family smoking habits by 103% (OR=2.03; 1.78-2.78). Also, presence of any 3 of the investigated risk factors within the family constitutes a crucial cut-off point that increases the individuals' coronary risk by 67% (1.67; 1.35-2.11, $P<0.01$) and discriminant analysis showed that score >3 allocate coronary patients with high accuracy (Wilks lamda = 0.881, $P<0.001$).
Conclusions: The application of the suggested family risk score could be a useful tool in the primary prevention of ACS, as well as in detecting and understanding associations between genetic vulnerability and cardiovascular risk factors.

P3617 Sex differences in cardiovascular risk factors and the risk of developing acute coronary syndromes: the CARDIO2000 study

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Background: Coronary heart disease (CHD) is markedly more common in men than in women. In this study, we analyzed the extent in which cardiovascular risk factors may influence the sex difference in CHD risk, in a Mediterranean population.
Methods: During 2000-01, we randomly selected from all Greek regions 848 hospitalised patients with a first event of an acute coronary syndrome and 1078 paired, by sex, age, and region controls, without any suspicious for CHD. In order to evaluate sex differences in the risk factors we developed multivariate risk models with respect to gender.
Results: Women patients were significantly older than men (65.3 ± 8 vs. 59.7 ± 10 years old, $p < 0.01$). The frequency ratio of males to females patients was 4 to 1. The effect of the family history of premature CHD on the risk of developing acute coronary syndromes seems to be related more consistent in males (difference in odds ratio: delta-OR = 1.93, $p<0.01$). The presence of hypertension affects more significantly females (delta-OR = 3.36, $p<0.05$), while hypercholesterolemia is associated with the coronary risk, more consistent in men (delta-OR = 2.58, $p<0.05$). The higher education level as well as the adoption of Mediterranean diet seems to be more protective in females (delta-OR = 0.47, and delta-OR = 0.16, respectively, $p<0.05$), while, depression is associated with higher risk of developing CHD in women (delta-OR = 1.35, $p<0.05$).
Conclusions: This study arose a marked difference in CHD risk between sexes. Lifestyle characteristics as well as several clinical symptoms or laboratory measurements seem to play significant role in the distinction of the risk factors profile between sexes. However, much remains to be learned about the mechanisms that relate CHD risk and sex.

P3618 The influence of previous participation in EUROASPIRE I on the performance of centers participating in EUROASPIRE II

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Introduction: In EUROASPIRE I (1995-1996), 9 European countries participated. The second EUROASPIRE II survey was conducted in 1999/2000 with the addition of 6 more countries. We investigated whether the centers involved in both the first and second survey (Group A) showed an overall different management of their patients (pts) compared to those participating for the first time in EUROASPIRE II (Group B).
Methods: The following parameters were compared: a) Information on risk factor (RF) history: Hypertension, hyperlipidemia, smoking, medication use. Measurment of height, weight, blood pressure (BP) on admission. b) Availability of similar data at discharge. c) Percentage of pts interviewed, 18 months later. d) At interview, advice about lifestyle modification efforts, and use of drugs.
Results: 1) When both hospital admission and discharge data were compared, Group A centers performed better in 18 indices of performance (A better in 14, B in 4, $p< 0.031$). Interview participation was also greater in Group A. 2) As regards lifestyle modification overall differences were NS. 3) When use of drugs at discharge and interview were compared, Group A increased â-blockers and ACE inhibitors more, while Group B statins. 4) Centers in Groups A and Group B had a similar GNI per capita, North/ South distribution and mean abstract submission to ESC Congress, 2000.
Conclusions: More experienced groups seem to perform better as regards hospital data management. However, the differences in lifestyle advice modification and drug use are not different among countries participating in both EUROASPIRE I and II vs those only in II. European harmonization of physician practices may be responsible for the latter finding.

P3619 Physical activity may prevent subsequent coronary events in unstable angina through autonomic nervous system modulation

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Background: Exercise training has assumed a major role in both the primary and secondary prevention of coronary heart disease (CHD). However, which mechanisms mediate these benefits is still a matter of continuing debate. This study sought to determine whether the intensity and frequency of recreational activity may influence autonomic nervous system balance, and exert possible benefits in high risk CHD pts.
Methods: Patients were selected from the "Studio sulla Prognosi della Angina Instabile" (SPAI; recruited 1999-2000), which was designed to assess factors able to early identify pts at high risk for subsequent coronary events. Only pts admitted to CCU with a diagnosis of rest unstable angina were enrolled in the study. Exclusion criteria were: previous history of CHD, low ejection fraction (<40%), diabetes mellitus and atrial fibrillation. Health habits, medical history, recreational and work-related total physical activity as recorded with a validated protocol were obtained at baseline and at 6 months follow-up. Vagal and sympathetic activity were assessed, at admission, by time domain measurements of heart rate variability (pNN5O and SDANN, respectively).
Results: Hundred five pts were followed for 6 months. 32 pts (Gr1) had a major coronary event (6 deaths, 8 non fatal acute myocardial infarction, 8 hospital readmission due to documented ischemic attacks, and 10 urgent CABG or PTCA). The remaining 73 pts showed good clinical outcome, and served as control (Gr2). Total weekly energy expenditure was stratified as low (<600 kcal/wk), moderate (600-1500 kcal/wk) or high (>1500 kcal/wk). Twenty of the 32 Gr1 pts (62%) expended less than 600 kcal/wk. Ten of the 73 Gr2 pts (14%) behaved similarly. Analysis of the heart rate variability showed that extremely low (<3%) values of pNN50 predicted mortality and total events. A pNN5O <3% was found in 18/32 Gr1 pts (56%) vs 2/73 Gr2 pts (0.8%). There was a significant relationship between kcal/wk and pNN50. These findings persisted after adjustment for other life-style variable. Conclusions. (1) A shift in the autonomic balance with a loss of vagal tone (pNN50<3%) may be observed in a great portion of pts having unstable angina and an adverse outcome. (2) This could be a reason for coronary vascular instability, and subsequent coronary events. (3) Even moderate physical activity is associated with favorable sympathetic-parasympathetic balance, and better CHD prognosis.

P3620 FLUVACS: flu vaccination in acute myocardial infarction. A pilot study

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Background: Previous studies showed that germ-free chickens infected with a herpes virus developed atherosclerotic lesions and that immunization with a turkey herpes virus prevented the development of atherosclerosis. Recent reports detected an increased number of patients (pts) with acute coronary syndromes (ACS) during the flu season. In addition, the World Health Organization recommended vaccination against Influenza infection for the Southern Hemisphere winter 2001.In the present study, we evaluated the impact of a preventive vaccination in acute myocardial infarction (AMI).Methods: A total of 200 pts admitted in the first 72 hours of an AMI were included in a multicenter prospective registry, during the winter season 2001 in Argentina. All pts received a standard therapy for AMI, 100 pts were allocated as Group A for a single unique parenteral vaccination containing A/Moscow/10/99-like virus, A/New Caledonia/20/99 (H1N1)-like virus, and AB/Sichuan/379/99-like virus. A control group of 100 pts were allocated as Group B. Exclusion criteria were absolute contraindication for vaccination and Killip Class D. Combined end points (death, reinfarction, and rehospitalization because of ischemia) were collected at 6-months follow-up. The comparison of categorical variables between the two groups was performed by means of the Mantel-Haenszel Chi squared statistic or the Fisher' s exact test.Results: There were 17% of ischemic events during the study. The first primary outcome - a composite of death, nonfatal AMI, or severe ischemia - occurred in 10% of the vaccine group and 24% in controls (relative risk (RR) 0.42; 95% confidence interval (CI) 0.21 to 0.83; P=0.008). The double end-point rates were 6% and 12% in A and B, respectively (p = 0.03). Cardiovascular death as a single end-point: RR with vaccine as compared with controls, 0.25; 95%, CI 0.05 to 1.15; p = 0.05.Conclusion: This study is the first to test the use of prophylactic influenza-vaccine in ACS showing a positive trend in reducing subsequent death and ischemic events in AMI.This could be related to an enhaced humoral immune response, particularly during flu season and may reflect a rapid migration of committed B-lymphocytes

P3621 Prevalence of patients with MADIT II risk factors in the prospective German PreSCD registry including 4565 post-myocardial-infarction-patients

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Objectives: The PreSCD-project (Prevention of Sudden Cardiac Death) is an ongoing prospective registry in Germany to determine the prevalence of patients (pts) post non-acute (>21 days) myocardial infarction (MI) under the cascaded level of risk defined by the MADIT I/MUSTT trials. Recently the MADIT II trial was terminated early by the Data and Safety Monitoring Board due to significantly reduced total mortality in favor of the ICD limb compared to conventional therapy. In contrast to MADIT I, pts surviving a previous MI were eligible for MADIT II without additional risk factors other than depressed left ventricular ejection fraction (LVEF) <= 30%. How many patients this represents is therefore an important clinical issue, and the aim of this subanalysis is to evaluate the prevalence of MADIT II type pts within the PreSCD-registry.
Methods: 40 physicians in private practice consecutively screen their post-MI-Pts according to combined MADIT I/MUSTT criteria: i.e. LVEF is evaluated for all patients with MI>21 days Pts with LVEF <= 40% undergo a 24-h-Holter-ECG, and those with non-sustained ventricular tachycardia (nsVT) are referred to electrophysiological (EP) testing (excluding those with treatable ischemia). Pts with ischemia undergo revascularization whenever possible and redo the screening cascade after procedures. Pts are followed up regularly at 6, 12, 18 and 36 months to determine any of the following events: death (cardiac, SCD, non-cardiac, unknown reason), syncope, resuscitation, Re-MI, PTCA, CABG, ICD implant or none of these. In case of EP-testing or ICD-implant detailed information on induction modes and occurrence of ICD-therapy is recorded.
Results: 4565 post-MI-pts were screened up to date with available LVEF-values. 240 (5.26%) of these pts presented with LVEF <= 30%. In 178 (74.2%) of pts with low LVEF <= 30% nsVT could be not documented, and therefore these pts were not referred to EP testing and further risk stratification. Less than 1% of all post-MI patients fulfill the criteria of MADIT I. In comparison, MADIT II patients are 5 times more frequent than MADIT I patients.
Conclusion: MADIT II patients are 5 times more frequent than MADIT I patients. Identification of these patients by practitioners is feasible using routine procedures.

BETA BLOCKERS IN HEART FAILURE

P3622 Efficacy and safety of carvedilol during initiation of therapy in patients with severe chronic heart failure: results of the COPERNICUS study

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Background: Despite their established utility, some physicians remain hesitant about using beta-blocking agents for the management of heart failure because of concerns that initiation of treatment produces few immediate benefits and carries important risks.
Methods: We evaluated the efficacy and safety of initiating carvedilol in a randomized placebo-controlled trial that enrolled 2289 patients with severe heart failure. Such patients are generally perceived to have the most difficulty being started on treatment with a beta-blocker.
Results: During the initiation and uptitration period (the first 8 weeks of the trial), the carvedilol group (CRV) had a lower instantaneous risk of death, death or hospitalization, and death, hospitalization or permanent withdrawal of double-blind treatment than the placebo group (PBO). The direction and magnitude of the effects during the first 8 weeks were similar to those observed during the entire study and were apparent even in a subgroup of high-risk patients with recent or recurrent decompensation or a very depressed ejection fraction. (Kaplan-Meier rates and Cox model hazard ratios (HR) are shown in the table below.) The differences in favor of carvedilol became apparent after 14-21 days of treatment. During the first 8 weeks, only one serious adverse event was reported with a frequency >2% (worsening heart failure), and it was reported with a similar frequency in the PBO and CRV groups (All pts: PBO 6.4% vs CRV 5.1%; high-risk pts: PBO 11.4% vs. CRV 8.8%).

		8 wk PBO rate (%)	8 wk CRV rate (%)	HR <8 wks	HR overall
All pts	Death	2.31	1.73	0.75	0.65
	Death or hospitalization	14.38	12.32	0.85	0.76
	Death, hosp. or perm. w/d	17.48	14.78	0.83	0.76
High-risk pts	Death	4.99	1.02	0.20	0.61
	Death or hospitalization	20.94	14.97	0.71	0.71
	Death, hosp. or perm. w/d	25.01	17.32	0.67	0.68

Conclusions: These findings do not support concerns about the efficacy and safety of initiating therapy with carvedilol in patients with chronic heart failure and provide the reassurance needed to encourage the high levels of use that are warranted by the results of clinical trials.

P3623 Carvedilol blunts the anti-natriuretic effect of norepinephrine in humans

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Activation of the sympathetic nervous system contribute to sodium retention in chronic heart failure (CHF). With beta-blockers use becoming more prevalent in treating CHF, the choice of drugs raises important theoretical and practical questions. The functional importance of the peripheral alpha-1-adrenergic blocking property of carvedilol has not been fully defined. In this study, we have tested the hypothesis that the alpha-1-adrenergic blocking property of carvedilol will blunt the anti-natriuretic effect of norepinephrine (NE) in humans. The effects of intravenous NE (0.075 ug/kg/min for 60 min) and carvedilol pre-treatment (25 mg bid for 7 days), alone and in combination, on urinary sodium excretion (UNaV), glomerular filtration rate (GFR) and segmental tubular function were studied in a single blind placebo-controlled cross-over 4 day study involving 8 healthy male subjects aged 25.5±0.3 years. All subjects were studied undergoing maximal water diuresis. Proximal tubular reabsorption was evaluated by estimation of the fractional excretion of lithium (FELi). NE alone decreased UNaV by 27% from 166±14 to 122±11 μmol/min ($P<0.05$) without altering GFR. FELi was increased by NE from 17±1 to 14±1% ($P<0.05$). Carvedilol pre-treatment significantly attenuated the fall in UNaV to only 10% from 146±9 to 131±10 μmol/min ($P<0.05$, placebo+NE versus carvedilol+NE). Carvedilol pre-treatment had a similar attenuating effect on the NE-induced increase in fractional reabsorption of sodium in the proximal tubule ($P<0.05$). The pressor response to NE was blunted by carvedilol pre-treatment ($P<0.05$). We have therefore shown that carvedilol is capable of blunting the anti-natriuretic effect of NE which suggests a functional importance for its alpha-1-adrenergic blocking property.

P3624 Increasing β-bockers prescription in a heart failure clinic

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B-Blockers (BB) and ACE inhibitors are the first line therapy in systolic heart failure (HF). Some authors suggest that 80 to 85% of the patients (pts) with systolic HF should be under BB. However the use of BB in clinical practice is still much less frequent as reported in the EPICA study and in the Euroheart Survey HF. Between 1996 and the end of 2000 BB were prescribed to 42% of the pts of our HF clinic. Logistical problems were the main reason for not reaching higher levels of BB prescription.

The present study tried to evaluate if during the period of one year we could increase the level of prescription of BB by giving a particular emphasis to the implementation of current HF therapy guidelines.

During 2001 we observed 179 pts with severe HF; 24 had no indication for BB according to the European Society of Cardiology guidelines. From the remaining 155 pts 122 (79%) were on, or initiated BB. This represented a very significant increase comparing to the prescription level registered until the end of 2000 (122 (79%) out of 155 pts vs 82 (42%) out of 195 pts; $p < 0.00001$). Carvedilol was the BB used in 99 (81%) of the cases. The age of the pts on BB was 50±12 years and 84% of them were males. Left ventricular ejection fraction (EF) was 29±8%; 86 (70%) of the pts were on NYHA class II or III. Ninety eigth percent were on ACE inhibitors.

The reasons for not using BB in the remaining 33 pts were: the presence of contra-indications in 13 (39%) pts (in 9 of them they were of a non-cardiac nature), NYHA unstable class IV in 1 (3%), fluid retention in 4 (12%), bad patient compliance in 2 (6%) and logistical reasons in 13 (39%).

In the everyday conditions of an outpatient heart failure clinic of a university hospital it is possible to significantly increase the level of prescription of BB during a one year period. We reached the target suggested by others. Logistic constraints and the presence of contra-indications were the main reasons that limited an even higher prescription of BB.

P3625 Left ventricular diastolic function and coronary flow reserve in low-symptomatic patients with dilated cardiomyopathy during bisoprolol therapy

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The aim of this study was to assess the degree of LV diastolic function by transthoracic Doppler echocardiography (TTE-DOPPLER) and to investigate coronary flow reserve (CFR) assessed using transoesophageal Doppler echocardiography (TEE-DOPPLER) in dilated cardiomyopathy (DC) patients (pts) treated with bisoprolol.

Material and method: The study population consisted of 19 pts (17 men), mean age 56±21 years, with DC and angiographically proven normal coronary arteries. In all pts, the LV inflow pattern at the level of the mitral anulus was assessed using TTE-DOPPLER method. The Doppler parameters: peak velocity of early diastolic LV inflow (E), peak velocity of late diastolic LV inflow (A) and E wave deceleration time (EDT) were measured at baseline. At rest and after intravenous infusion of dipyridamole (0.84 mg/kg/10 min), peak diastolic coronary flow velocities were measured in the proximal part of the left anterior descending coronary artery using TEE-DOPPLER. CFR was calculated as a ratio of maximal diastolic coronary flow velocity after dipyridamole infusion to maximal diastolic coronary flow velocity at baseline. Both examinations were performed before and 3 months after start of bisoprolol therapy.

Results: In the study group the E/A ratio after bisoprolol treatment was significantly higher compared to baseline examination 0.70 ± 0.09 versus 1.17 ± 0.2 ($p<0.05$). EDT significantly increased after bisoprolol therapy ($p<0.01$). The systolic CFR and diastolic CFR significantly enhanced after bisoprolol therapy (1.36 ± 0.16 vs 1.53 ± 0.17 -$p < 0.05$; 1.61 ± 0.17 vs 1.80 ± 0.19 - $p < 0.01$.

Conclusion: Three-months bisoprolol therapy leads to improvement of left ventricular diastolic function and coronary flow reserve in low-symptomatic pts with DC.

P3626 Carvedilol versus perindopril in idiopathic dilated cardiomyopathy

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Background: Both beta-blocking agents and ACE-inhibitors are standard therapy for heart failure. To evaluate their benefit individually and in combination on symptoms and left ventricular function we designed a protocol in which patients with NYHA FC II-III idiopathic dilated cardiomyopathy were randomised at baseline to a beta-blocking agent (Carvedilol) or Ace-inhibitor (Perindopril) and after 6 months commenced on the combination. Herein we report the 6 month data (Phase I).

Methods: In this prospective, randomised, open-labelled study we enrolled 59 consecutive patients with newly diagnosed idiopathic dilated cardiomyopathy in NYHA FC II-III. Patients were randomised to maximum dose of Carvedilol or Perindopril in addition to diuretics and digoxin. Echocardiograms, radionuclide studies, and NYHA FC were determined on admission and after 6 months of treatment.

Results: There were no differences in the baseline characteristics between the study groups. After 6 months 8 patients died (4 in each group) and 4 patients did not complete the trial for non-medical reasons. Left ventricular dimensions were reduced and radionuclide ejection fraction increased in the patients treated with Carvedilol. There were no changes in the Perindopril group (table).

	P (n=24) Baseline	6 months	p	C (n=23) Baseline		p 6 months
EDD (mm)	64 (8)	63 (6)	NS	66 (7)	62 (8)	0.005
ESD (mm)	55 (7)	54 (3)	NS	58 (8)	52 (11)	0.001
EF (%)	23.9 (9)	27.6 (9)	NS	21.4 (9)	33.3 (9)	0.0008
NYHA FC	2.5 (0.9)	1.9 (0.8)	0.005	2.6 (0.7)	1.6 (0.7)	0.0005

p=baseline versus 6 months within each group; values are mean (standard deviation); P=Perindopril, C=Carvedilol

Conclusion: Carvedilol monotherapy resulted in a sustained improvement of both symptoms and left ventricular function at 6 months. These results are encouraging and may suggest a new therapeutic approach in patients with idiopathic dilated cardiomyopathy.

P3627 Geographical variation in beta-blocker, spironolactone and digitalis use in chronic heart failure

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Background and Methods: There is now a strong evidence base, from large randomised trials, for the treatment of low left ventricular ejection fraction (LVEF) chronic heart failure (CHF). This evidence has been summarised in new international guidelines. Consequently, geographical variation in treatment should be less prominent than previously. We have examined variation in treatment practice in the 26 participating countries in the Candesartan in Heart Failure - Assessment of Reduction in Mortality and morbidity (CHARM) programme. CHARM Added randomised 2548 ACE inhibitor treated patients with a LVEF < 0.40 to placebo or candesartan. The 26 participating countries were grouped as follows: 1. Belgium, Netherlands, France, Luxembourg 2. UK, Ireland, Australia, South Africa 3. Czech Republic, Hungary, Poland 4. Germany, Switzerland 5. Norway, Denmark, Sweden, Iceland, Finland 6. USA 7. Canada. Italy/Spain/Portugal [n=50], Malaysia/Singapore [n=59] and Russia [n=15] were excluded from this analysis, because of small numbers. The table shows treatments used in CHARM Added.

Treatment (%)	Geographical region						
	1	2	3	4	5	6	7
number of patients	280	197	219	371	403	597	357
beta-blocker	56	32	59	74	55	57	50
spironolactone	23	12	22	15	13	15	17
digitalis	33	46	59	65	44	75	66

Conclusions: While the overall use of beta-blockers in CHARM is much higher than in prior CHF studies, there is still a surprising 2-fold or greater regional variation in use of these agents. There is similar variation in the use of spironolactone. Digitalis is now used no more frequently than beta-blockers.

P3628 Limited predictive value of cardiopulmonary exercise indexes in chronic heart failure patients treated with carvedilol

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Peak oxygen consumption (pVO2) derived during cardiopulmonary exercise testing (CPX) is a powerful predictor of mortality in chronic heart failure (CHF). Up to now, the prognostic role of CPX in CHF cohorts treated with b-blockers has not been addressed. Therefore, we studied 508 consecutive CHF patients (pts) who performed symptom-limited CPX with a peak respiratory exchange ratio (RER) >=1.05: mean age, pVO2, the rate of increase of minute ventilation per unit of increase of carbon dioxide production (VE/VCO2 slope) and left ventricular ejection fraction (LVEF) were 59±9 years 13.9±3 ml/kg/min, 32±2 and 25±7%, respectively. Composite end-point was death due to cardiovascular disease and urgent heart transplantation. Pts were divided according to carvedilol treatment (C and noC pts): 236 C pts (46%), with a mean dose of 25±13 mgr. Follow up lasted 856±541 days and 105 pts (21%) had major composite events. Multivariate analysis revealed VE/VCO2 slope, LVEF, pVO2, and C treatment as independent and additional predictors of cardiac events in total population (χ^2=64.2, 21.3, 9.7, 7.4, all with p=0.001), VE/VCO2 slope, LVEF, and pVO2 in noC pts (χ^2=44.2, 12.3, 7.2, all with p<0.001) and only peak VO2 in C pts(χ^2=7.5, p<0.01). As regards pVO2, pts were stratified into 4 groups: pVO2 <=10 ml/kg/min., >10 to <=14 ml/kg/min, >14 to 18 ml/kg/min and >=18 ml/kg/min:in the noC, total mortality rates were 55%, 28%, 26% and 0% respectively (p<0.0001) whereas, in the C group, total mortality rates were 26%, 11%,10% and 4%, respectively (p<0.05). Notably, in the 213 C pts with pVO2 >10 ml/kg/min, no significant difference in total mortality rates according to pVO2 classification was observed and no additional outcome indexes were selected.

Conclusions: in chronic heart failure patients treated with Carvedilol, pVO2 provides limited predictive information and no additional gas exchange parameters, i.e. exertional ventilatory response, yields supplementary prognostic advice.

P3629 Restoration of baroreflexes by slow controlled breathing and beta-blockade in heart failure patients

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Controlled breathing at a slow rate has been proposed as a therapeutic intervention in CHF patients because of its beneficial effects on chemoreflex function. On the other hand little information exists whether slow controlled breathing also favourably affects arterial baroreflex function, which in these patients is impaired and is associated with an adverse prognosis. Further issues that have not been clarified are whether beta-blocker treatment also potentiates the arterial baroreflex in CHF patients and whether such putative effect is additive rather than redundant to that of slow breathing. We therefore tested in CHF patients the effects of slow controlled respiration and/or chronic beta-blocker treatment on the bradycardic and depressor responses to carotid baroreceptor stimulation induced by neck suction.

In 10 CHF patients aged 60±1.4 yrs (NYHA class II-III, peak VO2 14.3±2.9 ml/min/kg, ejection fraction 31.0±1.9%), blood pressure (Finapres), RR interval (ECG) and respiration (impedance) were recorded beat-to-beat. Each patient was subjected to carotid baroreceptor stimulation by -40 mmHg neck suction obtained via a pneumatic collar and maintained for 90 sec; the stimulation was applied during spontaneous respiration as well as during slow controlled respiration (6 cycles/min). A repeat study during chronic treatment with carvedilol (25-50 mg/day) was obtained in 6 patients.

Baseline values of systolic blood pressure were 118.9±8.2 and 106.6±7.5 mmHg during spontaneous and slow breathing, respectively (p<0.01), the corresponding values of RR interval being 738±54 and 770±36 msec (p<0.05). Both the depressor and the bradycardic responses to neck suction were significantly larger during slow (-10.6±1.3 mmHg and +52.3±6.8 msec, respectively) than during spontaneous breathing (-4.7±1.6 mmHg and +28.1±6.3 msec, both p<0.01). The responses to neck suction were found to be enhanced during chronic carvedilol treatement and were even further enhanced when the carvedilol-treated patients were subjected to slow breathing (carvedilol: -10.9±3.1 mmHg, +76±9.9 msec; carvedilol+slow breathing: -17.4±2.2 mmgH, +120±26.1 msec).

In summary, in patients with CHF i) slow breathing as well as beta-blocker treatment restore the impaired arterial baroreflex function typical of this condition; ii) both the cardiac and the vascular components of the baroreflex are affected, and iii) the effect of these interventions on the baroreflex is additive so that combination of the two brings about baroreflex responses comparable to those seen in healthy subjects.

P3630 Application of carvedilol early after acute myocardial infarction prevents remodelling in patients with left ventricular dysfunction

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In order to evaluate the potential effects of carvedilol on reduction of LV mass and on LV remodelling after first myocardial infarction (AMI), sixty-five patients aged 46 ± 5 years with LV ejection fraction <45% were followed up for 6 months.

Methods: All of a.m. patients received streptokinase, aspirin and heparin in the acute phase of AMI. Thirty-one of them received carvedilol twelve hours after fibrinolysis in the initial dose of 3.125 mg twice daily and enalapril in the initial dose of 2.5 mg twice daily. The dose of carvedilol was increased to a maximum given dose of 25 mg twice daily at the end of the first month if the blood pressure was >110/80 and the heart rate was >55 beats per minute. The control group was made of 34 pts. who received only enalapril in the initial dose of 2.5 mg twice daily. In both groups the dose of enalapril was increased to a maximal given dose of 10 mg twice daily at the end of the first month. Echocardiography was performed before discharge (10 ± 2 days after admission) and at three and six months after AMI. LV wall thickness, chambre diameter, LV mass and LV ejection fraction were followed up.

Results: Systolic and diastolic blood pressures were significantly decreased at the discharge and at six months control in both groups. A significant reduction in heart rate was found in the carvedilol group in comparison at the discharge and at 6 months control (74 ± 14 vs. 65 ± 12 beats/min; p<0.001). Significant differences in heart rate between groups were also found (74 ± 14 vs. 81 ± 11; p<0.005 at discharge and 65 ± 12 vs. 74 ± 11; p<0.01 at six months control). Left ventricular non-infarcted wall thickness decreased in the carvedilol group (11.8 ± 1.2 vs. 12.5 ± 1.8 mm; p<0.01) at 6 months control. There weren't significant differences for this parameter in comparison of two groups at 6 months control. LV mass decreased both in carvedilol (275 ± 28 g vs. 245 ± 23 g; p<0.05) and in the control group (256 ± 31 g vs. 236 ± 22 g; p<0.05) at 6 months control (p=NS). LV ejection fraction increased in carvedilol group at 6 months (42 ± 5% vs. 52 ± 10%; p<0.05), while in control group we didn't find statistically significant improvement (40 ± 4 vs. 45 ± 6; p=NS).

Conclusion: Early application of carvedilol shows potential role in prevention of remodeling process in patients with LV dysfunction after AMI by decreasing the chambre diameter, reversion of LV hypertrophy and improving of LV ejection fraction.

P3631 The effects of alpha- and beta-blockade on ventilatory responses to exercise in chronic heart failure

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Background: Patients with chronic heart failure complain of exercise intolerance, usually due to breathlessness and fatigue as demonstrated by a reduction in peak oxygen consumption (pVO2) during incremental exercise testing with metabolic gas exchange analysis. There is also an increased ventilatory response to exercise as shown by an increase in the slope relating ventilation (VE) to carbon dioxide (CO2) production (VE/VCO2 slope). This is strongly linked to prognosis, but the cause of this abnormal ventilatory response is not clearly understood. It might be linked to the effects of the sympathetic nervous system on skeletal muscle ergoreceptors or central chemoreceptors.

Aim: The aim of the present study was to assess the influence that short-term alpha-and beta-blockade has on the ventilatory response to exercise and symptoms of breathlessness in patients with chronic heart failure and a group of control subjects.

Methods: 11 patients with chronic heart failure and 11 control subjects underwent repeated exercise testing with metabolic gas exchange after random, double-blind administration of either an alpha blocker and placebo, a beta-blocker and a placebo, both an alpha blocker and a beta-blocker or double placebo.

Results: Patients had a significantly lower pVO2 (20.7 (4.9) v 37.6 (9.6), p<0.0001), and a steeper VE/VCO2 slope (26.5 (4.1) v 37.1 (8.2), p=0.0011), than controls. The blood pressure at rest and at peak exercise was significantly lower in both patients and controls for the tests following alpha and beta-blockade (p<0.05) and there were lower gradients of the slopes relating heart rate to oxygen consumption during the tests following beta-blocker ingestion (p<0.05). There were no significant differences in exercise time or peak ventilatory variables following beta or alpha-blocker ingestion. The pVO2, VE/VCO2 slope and tidal volume at peak exercise were not different. There was a significant reduction in VE in the first two stages of exercise following the active medication. The combination capsule produced the greatest difference (P<0.005), but the alpha- and beta- blockers alone also reduced ventilation (P<0.05). There was no difference in perceived exertion during exercise for any of the capsules.

Conclusion: Acute sympathetic inhibition can reduce ventilation during exercise in patients with heart failure and control subjects.

P3632 Prediction of cardiovascular events in the patients with heart failure on beta-blocker therapy by haemodynamic and functional capacity assessment

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The prognostic value of the parameters commonly used in the patients with heart failure (HF) may be changed when they are assessed on beta-blocker (BB) therapy. One-hundred eighty-four patients with chronic HF (LVEF, 20±7%; peak VO2, 14.3±4.5 ml/k/min) were assessed by MUGA and cardiopulmonary exercise (ex) testing with invasive hemodynamic monitoring before and, in the 164 patients (89%) who survived, after 9-12 months of maintenance therapy with carvedilol (n=102; 41±17 mg/day) or metoprolol tartrate (n=62; 106±45 mg/day). Chronic BB therapy was associated with an improvement in NYHA class (from 2.68±0.56 to 2.03±0.76, p<0.00001), hemodynamic parameters and LV ejection fraction (EF) (from 20±7 to 29±13%, p<0.00001) without significant changes in peak VO2 (from 14.7±4.4 to 15.0±4.7 ml/k/min) or in the slope of minute ventilation to carbon dioxide production (VE/VCO2 slope) (40±12 to 39±12). During the 29±20 months of follow-up after the reassessment on BB therapy, 28 (18%) patients died, 16 underwent heart transplantation (Tx), 67 (41%) died or were hospitalized for cardiovascular reasons (CVhosp) and 58 (35%) died or were hospitalized for worsening HF (HFhosp). Using Cox multivariate regression analysis with the variables obtained before BB therapy, total mortality was significantly related to peak VO2 (p=0.0002) and serum creatinine (creat) (p=0.002); mortality+Tx was related to peak VO2 (p=0.002), NYHA class (p=0.004) and creat (p=0.007); mortality+CVhosp was related to peak VO2 (p=0.00005), CI (HR, 0.46; p=0.001), NYHA class (p=0.015) and atrial fibrillation (p=0.03) and mortality+HFhosp was related to peak VO2 (p<0.00001), CI (p=0.02) and LVEF (p=0.04). In contrast, when the variables obtained during BB therapy were used, total mortality was related to creat (p=0.005), VE/VCO2 slope (p=0.0086), age (p=0.027) and resting PWP (p=0.035); mortality+Tx was related to PWP (p=0.00005), VE/VCO2 slope (p=0.0003), creat (p=0.008) and NYHA class (p=0.02); mortality+CVhosp was related to NYHA class (p=0.005), PWP (p=0.007) and VE/VCO2 slope (p=0.02) and mortality+HFhosp was related to VE/VCO2 slope (HR, 1.05; p=0.004), the ischemic cause of HF (p=0.016), NYHA class (p=0.014) and LVEF (p=0.04). Thus, BB treatment may lower the prognostic value of peak VO2 and the prognosis of the patients on BB seems to be mainly related to renal function, functional class, PWP and the ventilatory response to ex.

P3633 Enoximone echocardiography for the evaluation of left ventricular contractile reserve in heart failure patients under chronic beta-blockade

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Background Recent studies suggest that inotropic reserve evaluated by dobutamine echocardiography is an independent predictor of survival in patients with heart failure. The inotropic response to adrenergic stimulation might be attenuated in patients receiving beta-adrenoceptor blockers. Enoximone is a positive inotropic agent that acts via selective inhibition of the cyclic adenoide monophosphate-specific phosphosdiesterase.
Objective To test the hypothesis that enoximone could represent a valid alternative for the evaluation of inotropic reserve in heart failure patients receiving chronic beta-blocker therapy.
Methods We studied 26 pts (mean age 58±10 years) with either idiopathic (n=20) or ischemic (n=6) cardiomyopathy. Mean left ventricular ejection fraction (LVEF) was 30±7%. Eleven pts were not receiving betablockers (group A); 15 pts were receiving carvedilol at the mean dose of 34 mg/day (group B). All pts underwent low-dose dobutamine and enoximone stress echocardiography in two consecutive days. Dobutamine was infused at incremental doses of 5, 10 and 15 μ/kg/min, with 10 minute steps. Enoximone was infused at the dose of 1.5 mg/kg, at the concentration of 2.3 mg/ml, over 10 minutes. Cuff blood pressure and a three lead electrocardiogram were continuously monitored; LVEF was measured and colour tissue Doppler (in 4 and 2-chamber projections) was recorded before the test and at each step of infusion. Tissue velocities were obtained by analysing off-line the mean velocity profiles at the level of the annulus (septal, lateral, inferior and anterior) and at the level of basal and medium segments of septum, lateral, inferior and anterior walls.
Results LVEF increased by a similar extent with dobutamine and enoximone in both groups (respectively +9.6 vs +8.7 units in group A and +7.5 vs +8.9 in group B, NS). Dobutamine increased tissue Doppler velocities more than enoximone in 5 out of 12 segments in group A (lateral medium, inferior annulus, inferior basal, anterior annulus and anterior basal); the two drugs had similar effects in group B. Dobutamine induced non-sustained ventricular tachycardia in 3 patients and supraventricular tachycardia in 1, while enoximone did not induce repetitive arrhythmias.
Conclusions Enoximone proved to be as potent as dobutamine in evaluating the inotropic reserve of heart failure patients receiving chronic beta-blocker therapy. The absence of arrhythmias and the major feasibility of the test makes it preferable for such purpose.

P3634 Myocardial contractile response under low dose dobutamine identifies chronic heart failure patients who take benefit from Carvedilol

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Background: β-blockers (BB) like Carvedilol improve survival and reduce hospitalization rate in chronic heart failure (CHF) by improving left ventricular ejection fraction (LVEF). However, Carvedilol acutely reduce LVEF by pharmacologic withdrawal of adrenergic support to the failing heart. Clinical baseline data are not able to appreciate the LVEF improvement with Carvedilol. We want to see if myocardial viability, as determined by low dose dobutamine stress echocardiography (LDDSE) will predict EF improvement with Carvedilol.
Methods: 100 patients with Class II/III CHF were studied with LDDSE prior to receiving treatment with Carvedilol.. Contractile reserve was defined as a change in LVEF before and with dobutamine > 20%.LVEF was measured before introducing Carvedilol and 6 month after optimal dose reached. Group A contains patients with myocardial contractile reserve (N=59), group B patients without contractile reserve (N=41). Death or CHF hospitalization and improvement of LVEF with Carvedilol were measured in the two groups
Results: The two groups showed comparable rest LVEF, Heart rate and Arterial pressure. Patients in group A had lower BNP plasma level and higher 6 minute walk test performance.
In multivariate analysis (Age, rest LVEF, MCR, rest E/A ratio, rest Heart rate, Systolic arterial pressure, BNP plasma level, 6 minutes walk test performance), the sole existence of MCR could predict the improvement of rest LVEF under Carvedilol treatment in patients with chronic heart failure (p<0,0001). At the end of the follow up, hospitalizations and mortality is lower in group A than in group B (respectively p<0,04, p<0,01)
Conclusions: Presence of contractile reserve with low dose dobutamine stress echocardiography predicts improvement in LVEF with β-blocker therapy (Carvedilol) in patients with CHF. dobutamine stress echocardiography could help to detect patients who will take the best benefit with β-blocker therapy in term of mortality, morbidity and LVEF.

PREVALENCE AND POPULATION SURVEYS IN HEART FAILURE

P3635 Hospitalization for heart failure in the aging population. The analysis of Trieste database (1997-2000)

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Background: Since 1995, the reimbursement of hospital healthcare expenditure in Italy has been based upon the so-called Diagnosis Related Groups (DRGs). The DRG 127 includes all the cases in which the main clinical diagnosis is "heart failure (HF) or shock" and, therefore, it can be used to obtain epidemiological data concerning HF. The analysis appears to be of relevant interest, since in the district of Trieste the phenomenon of progressive aging of general population is very pronounced.
Methods: In this study, we evaluated the epidemiological data and clinical outcome of patients hospitalised for DRG 127 in the district of Trieste from 1997 to 2000 (5556 hospital admissions and 69236 days of hospital stay), using the database of the regional health system.
Results: The DRG 127 accounted for 2.6% of total hospital admissions and for 4% of total days of hospital stay; moreover, it resulted the first cause of hospitalisation for medical DRGs (18%) as well as the first cause of hospitalisation and days of hospital stay for cardiovascular DRGs (27.5 and 40.5%, respectively). Seventy-two percent of patients admitted for DRG 127 was older than 75 years. In 1997, a mean of 4/1000 inhabitants of the district of Trieste were hospitalised for DRG 127 (4.6 hospital admissions and 63 days of hospital stay/1000 inhabitants). Over the four years, the number of hospital admissions for DRG 127 increased by 20.3%, the days of hospital stay by 11.1%, and the related healthcare costs by 36.7%. Most of patients (89%) were admitted in Internal or Geriatric Clinics. By using suitable corrective factors, the prevalence rate of heart failure in 1997 was estimated as 6.4‰ (<65 years: 1.8‰, 65-74 years: 10.3‰, 75-84 years: 22.3‰, >84 years: 47.4‰). Based upon the first hospital admission, the incidence rate was estimated as 2.4‰ (<65 years: 0.8‰, 65-74 years: 2.2‰, 75- 84 years: 9.3‰, >84 years: 20.4‰). In-hospital, 1, 2 and 3-year survival rates from first hospital admission for HF were, respectively, 92, 80, 68 and 56% and was significantly affected by the age of patients. The most frequent aetiology was the ischemic heart disease (IHD)(50%), followed by hypertensive (26%) and valvular (7%). IHD showed the worst prognosis (3-year survival of 44%).
Conclusions: The analysis of the hospitalisations for DRG 127 in the district of Trieste may contribute to outline the national epidemiological scenario and the healthcare demand for HF in the next decades, and may be useful to plan effective models of integrated home-hospital care for the increasing number of affected subjects.

P3636 The coronary sinus anatomy in patients with advanced heart failure – A European registry

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Cardiac resynchronization therapy can be complicated by unusual coronary sinus (CS) anatomy.
Methods: This European registry studied the efficacy of a new series of 5 Guide Catheters (GCs) used with the endocardial EASYTRAK (EZT) over-the-wire left ventricular lead (GUIDANT, St-Paul). The clinical and anatomical parameters of the Coronary Sinus (CS) were studied within this registry.
Results: The 256 implants have been performed in 117 European centers by electrophysiologists, PTCA experts, and cardiac surgeons. All patients presented symptoms of heart failure of NYHA 3.0±0.6 with a left ventricular ejection fraction of 25±7%, and a cardiothoracic index of 57±8%. Some 80% were male and the mean age was 69 years. The CS ostium position in anterior-posterior view was in mid position for 55%, low for 39%, and high in 6% of patients. The CS ostium position in left anterior oblique incidence was 61% and 39% for proximity to the tricuspid valve, and more posterior toward the inferior vena cava, respectfully. The CS orientation is listed in the table.

CS orientation	% of patients
Horizontal	16
Steeply upwards	40
Angulation	29
Siphon	4
Early Bifurcation	7
Other	4

Conclusion: This registry has demonstrated that 85% of patients suffering from advanced heart failure have only 3 main CS orientations, and 15% of patients have another orientation.

P3637 The Euroheart failure survey: the value of the electrocardiogram in the evaluation of heart failure

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Background: The 12-lead ECG may be helpful as a way of excluding heart failure (HF), as a means of diagnosing its cause and to assist in making key therapeutic decisions such as the need for anticoagulation or cardiac resynchronisation.
Aims: To describe the ECG abnormalities relevant to clinical practice in an epidemiologically representative group of patients with suspected HF included in a large international survey.
Methods: In 25 countries belonging to the ESC, the EuroHeart Failure survey screened >40,000 hospital deaths and discharges from medical wards and identified >11,000 patients with suspected HF. 45% were reported to have moderate or severe left ventricular dysfunction. 14% died during 12-weeks follow-up. Copies of ECG's were requested from all patients and were read in a core laboratory (Kingston-upon-Hull) by a group of cardiologists. ECG measurements (time intervals, S&R wave height in leads V1&V6, septal q-waves) were made manually using calipers and each ECG was clinically reported.
Results: 800 ECG's have been reported so far; 5,000 will be reported by August. Clinical reporting revealed 2.9% of ECGs that were classified as normal and 38.6% classified as minor abnormalities only, whilst 31.6% had Q-waves consistent with a myocardial infarction. 67.2% of patients were in sinus rhythm, 25.8% in atrial fibrillation, 4.9% with paced rhythm and 2.1% in atrial flutter. The mean RR, PR (sinus rhythm only), QRS and QT intervals were 771 msecs, 142 msecs, 109 msecs, 378 msecs respectively. The proportion of patients with QRS >150msec, >130msec and >120msec were 9.9%, 18.3% and 24.5% respectively. 8.6% had voltage criteria for left ventricular hypertrophy.
Conclusions: This is the first large, international study of the ECG in suspected heart failure in a representative population of patients with heart failure. A normal ECG is uncommon; ECG abnormalities are common and should be an important guide to diagnosis and therapeutic decision-making.

P3638 Differences between genders in patients with heart failure

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Elderly women with heart failure represent a high percentage of hospital admissions by this prevalent pathology. Little is known about this population, although in the past decade several studies have shown that the clinical manifestations and prognosis in women with heart failure could differ significantly from those of men. In most of recent clinical trials of medical therapy for heart failure less than 25% of patients enrolled were women.
Objective: to evaluate differences between men and women with heart failure in psycosocial factors, comorbidity, aetiology and management.
Patients and methods: This study was planned from the Working Group on Heart Failure in the Spanish Society of Internal Medicine. The registry involved 50 hospitals all over Spain. Patients suffering this pathology and admitted in Internal Medicine Departments were studied. The data were obtained checking the clinical history and interviewing the patients from October 2000 to February 2001.
Results: The sample included 2145 patients who were age-matched. The patients median age was 77,2 ±10,5 years. 57,3% were women (median age 78,8) and 42,7% were men (median age 75,12). The percentage of illiterate and low cultural level women was significantly higher than in men, as well as the number of women with impaired physical and cognitive functions. There was a high comorbidity but there were different patterns (more hypertension and diabetes for women, and chronic lung disease and chronic renal failure significantly higher in men). The aethiology was unknown in more women than in men in the group of patients older than 77 (42,3% vs 32,7%). The underlying aethiologies in women were hypertension and valvular heart disease. Echocardiography was not performed before the admission mainly in old women (62,9%women vs 55,2%men $p<0.05$) and the eyection fraction in women was significantly higher than in men. Clinicians use more loop diuretics and digoxin and less spironolactone, betablockers and ACEIs in women than in men.
Conclusion: Women hospitalized for Heart Failure in Internal Medicine Departments have a different profile than men, and they are managed in a different way in clinical practice, far from current guidelines and trials.

P3639 Sleep apnoea in chronic stable heart failure: prevalence in general cardiology practice

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Background Estimates of the prevalence of sleep disordered breathing in patients with chronic stable heart failure vary widely (40-82%). Also these estimates come from selected cases in specialist units and may not be representative. The mechanism for the overwhelming majority is central rather than obstructive apnoea. The diagnosis of central sleep apnoea confers an adverse prognosis, possibly because sleep disruption and hypoxia lead to an increase in circulating catecholamines.

Method We aimed to measure the prevalence of apparently asymptomatic sleep apnoea in patients with chronic stable heart failure in a general cardiology practice. We performed overnight oximetry on 20 consecutive patients with stable heart failure, admitted to hospital for a variety of clinical reasons. All were NYHA Class II-III and had an EF<40%. Those with known abnormal sleep patterns, BMI >30 or signs of pulmonary disease were excluded. Age range was 35 – 74 yrs, male sex predominant (80%) and aetiology IHD (60%) or idiopathic DCM (40%). All patients were taking ACE inhibitors, 80% diuretics and 60% beta-blockers. We used a mean dip rate (desaturation > 4% from baseline) of >15/hr to diagnose sleep apnoea.

Results Mean EF was 23% (SD±8) and both mean FEV1 & FVC were >80%. Overall 30% of patients had sleep apnoea, with a mean dip rate of 21.4 (SD±7) dips/hr. Patients fell into two clearly separate groups. In those with apnoea the dip rates ranged from 16 to 35/hr; in those without dip rates were uniformly below 10 (mean 4.3 (SD±2.7))dips/hr. We did not identify any correlation between Epworth (daytime sleepiness) scores (mean 10.6 (SD±2.7)) and sleep apnoea in this relatively small patient group of whom 80% were NYHA Class III.

Conclusion In general cardiology practice sleep apnoea is prevalent in heart failure patients, with no obvious evidence of sleep disordered breathing, and the diagnosis is of prognostic relevance. Evidence is accumulating that treatments for central sleep apnoea improve symptoms, cardiac function and result in a reduction in circulating catecholamines. Identification of patients for formal sleep studies using pulse oximetry is straightforward and should be considered part of non-invasive assessment.

CARDIAC ASSIST DEVICES

P3640 Predictors of survival for patients treated with aortic balloon counterpulsation (IABP)

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Patients treated with IABP represent a selected high risk subset. We used multivariate logistic regression to analyse the prospectively collected data in the international Benchmark registry. The major predictors of in-hospital mortality for 21102 patients treated with IABP in 243 institutions between 1997 and 2001 were assessed, and are listed in the table. 13801 patients underwent cardiac surgery (mortality 18.9%), 5155 percutaneous coronary intervention (mortality 18.6%) and 2146 were treated medically (mortality 32.9%).

Odds ratio for major mortality predictors (95% CI)

	surgery	PCI	Medical
age > 75	1.5 (1.4-1.7)	2.2 (1.8-2.6)	2.0 (1.6-2.6)
previous CABG	1.8 (1.6-2-6)	0.8 (0.6-1.0)	1.0 (0.7-1.3)
cardiogenic shock	2.8 (2.5-3.1)	2.7 (2.3-3.1)	2.6 (2.2-3.1)
periph vasc. disease	1.5 (1.3-1.7)	1.4 (1.1-1.8)	1.3 (0.9-1.8)
unstable angina	0.4 (0.4-0.5)	0.5 (0.3-0.6)	0.5 (0.4-0.6)
LVEF < 30%	1.2 (1.0-1.3)	1.5 (1.2-1.9)	1.6 (1.2-2.2)
3 vessel disease	0.7 (0.6-0.8)	1.6 (1.4-1.9)	1.1 (0.9-1.4)
wean from bypass	1.6 (1.5-1.8)	-	-
preoperative IABP	0.5 (0.5-0.6)	-	-
IABP later than 5 days after admission	1.6 (1.4-1.7)	1.3 (1.0-1.8)	1.7 (1.2-2.3)
non-US institution	1.2 (1.0-1.3)	1.6 (1.3-2.1)	1.9 (1.4-2.6)

The model had a concordance of 74.9%, 78.6%, and 74.3% respectively for the three treatment categories.

Hospital mortality in patients treated with IABP was markedly higher when no intervention was performed. Several baseline clinical characteristics, as well as IABP timing relative to hospital admission and surgical intervention were identified as in-hospital mortality predictors. For some of these, there were major differences according to the mode of therapy that was chosen.

P3641 Superior outcome of ambulatory care versus hospitalization in patients on mechanical circulatory support

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Anticipating the increased necessity of long-term mechanical circulatory support (MCS), a policy to discharge patients home was introduced at our institution in 1996. This concept was followed for patients with intact psychological, social and family situation after full peripheral organ restitution. The study compares the results of these outpatients with MCS to those of a group of patients remaining hospitalized for non-medical reasons.

We report our 10-year experience with 108 patients on MCS, who were supported for more than 3 months. Group A consisted of 38 patients (25 Novacor, 13 Berlin Heart), with assist implantation from 1996 to 2001. They had a mean support time of 454 days (range 100-1074 days) and spent 326 days (range 20-769 days) at home. Group B consisted of 70 patients (24 Novacor, 46 Berlin Heart), with assist implantation between 1991 and 2000. They had a mean support time of 234 days (range 95-795 days) and were not discharged from hospital for psychological, social and familial or non-medical reasons. Complications, hospital readmissions, causes of death including infections and thromboembolic and bleeding events were recorded.

In group A total mortality was 16% (6/38). Two patients died from cerebral embolism, one from cerebral hemorrhage, two from systemic infection and one from multiorgan failure.

Thirty-two patients (84%) required 95 readmissions to the hospital (cerebral embolism (n=9), bleeding (n=1), wound infections (n=23), coagulation disorder (n=13), for heart transplantation (n=5) and non-cardiac causes (n=44)). There were no deaths related to device failure and only four patients had to be readmitted due to a minor MCS problem.

In Group B the mortality was higher at 43% (30/70; p=0.004 vs. Group A). This was largely attributed to the higher rate of infections (n=14; p=0.04 vs. Group A). Other causes of death were cerebral embolism (n=5), cerebral hemorrhage (n=7), and multiorgan failure (n=4).

In our experience ambulatory care of MCS patients proved advantageous in terms of mortality and incidence of infections. Ambulatory care has proven to be a safe therapeutic concept ensuring increased mobility and quality of life for patients on MCS and a reduction of the cost of treatment.

P3642 First use of the Orqis™ Medical Cancion™ Cardiac Recovery System (CRS) for heart falure therapy

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A new concept of mechanical unloading the heart has been invented to effectively decrease LVEDP, LVEDD, PCWP. A pilot clinical trial has been initiated in Austria. We report from the first clinical use of the Orqis™ Medical Cancion™ CRS

Methods: The CRS is connected to circulation via a graft cannula anastomosed to the left axillary artery and a percutaneous cannula placed into the left common femoral artery. Using a centrifugal pump, flow is initiated from the femoral to the axillary artery.

Results: A sixty-four year-old patient with chronic congestive heart failure, renal insufficiency, awaiting heart transplantation was admitted due to worsening symptoms. He was placed on dobutamine 16 μ/kg/min without obvious signs of improvement. Cardiac catheterization showed PCWP of 28 mmHg, CI 1.5 l/min/m^2. He had signs of worsening renal function with a BUN of 50 and a creatinine of 1.9 mg/dL. CRS was implanted and the patient was supported for 3 days. The system was electively explanted. There was a dramatic decrease in PCWP, LVDD and creatinine, as well as an increase in CI and EF, with maintaining low flows of 1.3-1.9 l/min.

		baseline	8h	24h	72h	24h post expl.	35 days post explant
PCWP	mmHg	28	22	10	9	7	7
CI	L/min/m^2	1,5	3,2	2	2,7	2,4	1,83
ABPm	mmHg	65	69	66	67	62	67
BUN	mg/dl	50	-	29	30	48	47
Cr	mg/dl	1,9	-	1,1	1,1	1,1	0,9
EF	%	25	35	n/a	n/a	n/a	30
LVEDD	cm	6,78	6,16	n/a	n/a	n/a	6,6

Conclusion: In this first patient the Orqis™ Medical Cancion™ CRS seems to be an effective system to quickly improve hemodynamics. Due to it's advantages such as easy and fast application of mechanical circulatory support this system may become an excellent short-term alternative for high-dose inotrop therapy. Additionally, it's application may delay applications of more invasive forms of mechanical circulatory support.

P3643 Ventricular tachyarrhythmias in patients with ventricular assist devices as prognostic indicator for survival

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Background: Ventricular tachyarrhythmias (VT) are associated with ventricular assist devices (VAD). The presence of VT has important implications in management and prognosis. This report is aimed to describe the association between VT and VADs and clinical outcome.
Methods: A study comprising of review of records of patients (pts) with VADs, for the presence of VT, indication for VAD support, and outcome was performed. Three commercially available VADs: Novacor (Worldheart, Inc., Ottawa, Ontario), Heartmate (Thoratec Corp., Pleasonton, CA), and BVS 5000 (Abiomed, Inc., Danvers, MA) were used. The indication for Novacor and Heartmate insertion was a bridge to transplantation in pts with chronic heart failure and that for BVS 5000 insertion was acute refractory cardiogenic shock. The pts with Novacor and Heartmate devices were included in Group A and those with BVS devices in Group B.
Results: A total of 98 pts underwent VAD insertion between 1993 and 2001. Group A (n = 43), included 27 pts with Novacor, and 16 pts with Heartmate VADs and Group B included 55 pts with BVS VADs. In this cohort, 88 (90%) pts had VT, 66 (75%) with non-sustained VT and 22 (25%) with sustained VT. In Group A, preexisting VT was present in 22 (51%) pts, all treated with anti-arrhythmics and/or ICDs, and 10 pts developed VT following LVAD insertion, requiring anti-arrhythmics in all and ICD implantation in 3 pts. In Group B, 44 pts (80%) had VT, all requiring anti-arrhythmics and none received ICD. Of the 22 pts with sustained VT, 15 pts (68%) (5 in Group A and 10 in Group B), required insertion of a right ventricular assist device (RVAD). None of these pts survived. Eighty percent of pts in Group A compared to only 40% in Group B were discharged home following either native cardiac recovery or transplantation.
Conclusions: (1) VT is present in the majority of patients who require LVAD implantation. (2) Following LVAD implantation, the presence of sustained VT needing RVAD support is associated with a poor prognosis. (3) Prognosis of patients with acute refractory cardiogenic shock is very poor despite LVAD support.

P3644 Clenbuterol structural, functional and molecular changes in a large animal model: relevance to usage of left ventricular assist devices

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Background: - Chronic hemodynamic off-loading with left ventricular assist devices (LVAD) is associated with regression of pathological hypertrophy. We have previously shown that clenbuterol (Clen), a beta2-adrenoceptor agonist stimulates 'physiological' myocardial hypertrophy in rodents and are exploring its potential as a novel strategy to maximize the efficacy of LVAD as a bridge to recovery. This study aims at evaluating the functional, morphological and molecular features of clen induced myocardial growth in a large animal model.
Methods: - 14 sheep were randomly assigned to treatment with either saline (n=7) or clen (n=7) for 6 weeks. Right ventricular (RV) pressure-volume loops were obtained before and after treatment, using micromanometer-conductance catheters. RV tissues were harvested at final assessment for: 1) Morphometric analysis of fibrous tissue. 2) Quantification of sarcoplasmic reticulum Ca^{2+}-ATPase 2A (SERCA 2A), phospholamban (PLB), sodium/calcium exchanger (NCX) and apoptotic markers by Western Blot. 3) MMP-2 and -9 activities by gelatin zymography. Serum samples were collected at final assessment for measurement of matrix metalloproteinase-1 (MMP-1), tissue inhibitor of metalloproteinases-1 (TIMP-1) and MMP-1/TIMP-1 complex.
Results: - RV wall thickness and heart weight were significantly greater in the clen treated animals. Systolic function was higher in the clen treated animals associated with a reduction in fibrous tissue in the myocardium. However, there was no significant difference in the myocardial protein expression of SERCA 2A, PLB, NCX, Bcl-2 family of proteins and caspases 3, 8 and 9. The MMP-2 and -9 activities and serum levels of free MMP-1 and TIMP-1 were also not different between the two groups.
Conclusion: - Clen produces 'physiological' cardiac growth. This supports its usage to maximize the efficacy of LVAD as a bridge to recovery.

P3645 S100A1: a marker for successful transformation of circulatory assist skeletal muscle ventricles (SMV's) for the failing heart

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Background: Biomechanical circulatory assist devices like autologous skeletal muscle ventricles (SMV's) have been considered as an attractive alternative treatment of chronic heart failure. Despite the profound loss of mechanical performance that occurs after exlusive electrical conditioning, recent advances in adaptation of SMV's to hemodynamic load by systemic pharmacological and dynamic-training interventions dramatically enhanced their mechanical performance (Biomechanical Hearts (2001), Guldner et al., Circulation 104). As Ca^{2+} cycling governs contraction we sought to explorate the molecular alterations underlying succssesful skeletal muscle transformation in SMV's by investigating the putative shift in the expression pattern of proteins that are involved in intracellular Ca^{2+} handling and contraction.
Methods/Results: In adult goats, SMV's were constructed as biomechanical hearts (BMH) from latissimus dorsi (M.lat.dorsi.) to pump volume against systemic load in intact circulation. Dynamic adaptation of SMV's was supported by combined dynamic training under electrical stimulation and systemic clenbuterol administration (50 μg/d). Samples of M. lat. dorsi from six goats were taken both prior to SMV construction (day 0) and at termination of experiments while samples from the contralateral M.lat.dorsi served as temporal controls. Western-Blot experiments from homogenates were carried out to investigate the expression levels of S100A1, SERCA2, SERCA1, PLB, cardiac and skeletal muscle actin. The most prominent shift in protein expression from day 0 to SMV and contralateral control at termination was found for the non-fatigue muscle specific Ca^{+} binding protein S100A1 (+29.5±7.1-fold, $P<0.01$, n=6) beside upregulation of SERCA2a (+5.2±1.3-fold, $P<0.01$, n=6), PLB (+2.7±0.9-fold, $P<0.03$, n=6) and cardiac-actin. In contrast, SERCA1 (-8.5±2.4-fold, $P<0.05$, n=6)and skeletal muscle actin was found to be significantly downregulated in SMV's compared to control.
Conclusion: Our results suggest that advanced dynamic and pharmacological training of fast skeletal muscle (Typ II) to BMH is based on the transdifferentiation into non-fatigue skeletal muscle (Typ I) as indicated by the shift in Ca^{2+} sensing and Ca^{2+} cycling proteins. Among these alterations most prominent changes occurred in S100A1 protein expression that might be therefore considered as an interesting marker for successful BMH generation.

P3646 Third generation of mechanical cardiac assist systems as long-term supporting devices for patients with heart failure

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Although there has been progress in the technique of pulsatile implantable ventricular cardiac assist devices (VAD) within the last 15 years they are still bulky (> 600 ml) and heavy (> 600 g) and therefore carry an inherent risk for complications. Pulsatile axial flow pumps of the latest generation are small (< 100 ml) and light (< 200 g). In an industrial joint venture an axial flow pump (INCOR) for long-term application (years) was developed. Due to magnetic levitation of the spinning rotor this device has no mechanical friction and therefore no wear at all (1), changes of the rotational speed of the rotor within one cardiac cycle create a pulsatility that is comparable to the physiological pulsating flow of the native heart (2), and the flow of the pump automatically adapts to the patient's need (3).
The VAD was evaluated in 14 calves to test hemolysis and thrombogenicity in short- and long-term observation. Five of the animals died within 12 hours after placement due to persistent ductus Botalli which was not anticipated and therefore overlooked in the first animals. One animal died due to slip-off of the outflow cannula which was only insufficiently connected to the pump. Six animals were euthanized after 40 days of support due to the requirements of the European approval authorities. One animal was euthanized after 150 days of support and one is still on the device (> 200 days). Clinically, no signs which could have been related to thromboembolic events were observed. Mean flow and power consumption were constant over the whole observation period. Plasma free hemoglobin was slightly elevated for a period of 1 week after operation, as was LDH. Both parameters normalized thereafter and remained constant. Fibrin degradation products did not show any increase. Creatinine and urea were normal at the time of placement and remained in the normal range. At explantation no thrombus deposit inside the cannulas or the pump was found. However, at the inflow site of one pump some fibrin deposits were seen which were related to poor polishing of the titanium surface. Additionally, in one of the calves' kidneys signs of a thromboembolic event could be seen. No further biological abnormalities could be detected during this pre-clinical trial. With regard to the pump, no pump stop or malfunction of the pump could be observed. The overall test results of this axial-flow blood pump are very encouraging. They have to be confirmed in a clinical trial which will start in March 2002.

P3647 Comparison of IABP and the new Jomed Reitan catheter pump in acute mitral regurgitation

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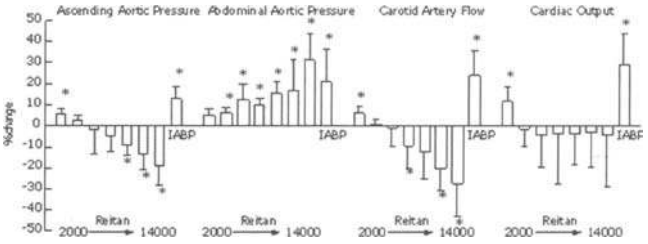
Background The Jomed Reitan Catheter Pump (RCP) is a new, minimal invasive, propeller based intra aortic device, designed to reduce left ventricular afterload. In this study the RCP was tested, placed in the high descending aorta, and compared to IABP in an acute mitral regurgitation (MR) animal model.

Methods In nine calves acute MR was created by placing a steel wire cage in the mitral valve. The RCP was tested at 2000 to 14000 rpm and compared to 1:1 IABP support. Cardiac output, coronary blood flow, carotid artery flow, ascending and abdominal aortic pressure, left atrial pressure and LV pressure-volume loops were recorded.

Results The RCP caused a large reduction in afterload (-28%, p<.001) at 14000 rpm. In the mean time, preload decreased (-20%, p<.001) and cardiac output remained the same. PV-loops shifted leftward and reduced in size, suggesting acute LV remodeling and a reduction in stroke work. The RCP redistributed blood from the upper to the lower body as seen by a reduction in carotid artery flow (-28%, p=.002) and an increase in mean abdominal aortic pressure (+32%, p<.001) (see Figure). The IABP increased cardiac output (+30%, p=.005), carotid flow and aortic pressure (see figure).



Mean perc. change in hemodynamics.

Conclusions The RCP is a very powerful afterload reducing device. In this acute MR animal model, it favored blood flow distally from the device and remodeled the left ventricle, but left out positive effects on cardiac output. Further research activities are planned to test the RCP in other aortic positions and types of heart failure, such as ischemic failure.

P3648 First prolonged use of the Thoratec heart mate II left ventricular assist device as a bridge to recovery

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The Heart mate II is an impellar pump capable of providing full circulatory support and virtually complete unloading of the left ventricle (LV) with flows of up to 10 L/min, making it possibly an ideal tool for bridge to recovery. However, to date, experience with prolonged use of the device, its effect on the heart and target organs, effect of lack of pulsatility and the type of antithrombotic therapy has been unknown. We describe our experience with the use of the device in a 41 year old man with a 4 month history of rapidly deteriorating heart failure due to idiopathic dilated cardiomyopathy. At the time of implantation the patient had a cardiac index of 1.7 L/min/m^2, PCWP of 33mmHg, with deteriorating renal and hepatic function. The device was placed behind the left costal margin without opening the peritoneum. The patient was weaned off CP bypass without difficulty. In the post-operative period the device maintained an output of 4-7L with the mean RPMs varying from 9-11000. Arterial pressure was 70mmHg with a flat trace. Kidney function improved immediately. Antiplatelet and antithrombotic therapy, which included aspirin and low molecular weight heparin, were started on the 2nd day, long term Warfarin was not used. There were no thromboembolic complications during the 160 days on the device. Initially, the pump was run in the automatic mode, which produced flows in excess of 7L and was occasionally associated with collapse of the left ventricle and multiple ventricular ectopics and runs of ventricular tachycardia. This responded to running the pump in the fixed mode. The patient was treated by additional pharmacologic therapy to induce reverse remodelling, followed by physiologic hypertrophy as part of the Harefield recovery protocol. The criteria for explantation were met significantly earlier than in patients receiving the Heart Mate I device. Following explantation, the patient made a smooth recovery and is being followed up, with evidence of maintained LV recovery to date. It is concluded that the Heart Mate II is a promising clinical tool, particularly for recovery.

THERAPEUTIC INTERVENTIONS FOR HEART FAILURE

P3649 Possible role of nitric oxide (NO) in preserving pulmonary diffusion capacity for carbon oxide (DLco) in heart failure (HF) patients

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Diffusion capacity of alveolar-capillary membrane (clinically expressed as diffusion for carbon monoxide) is impaired in HF patients. During exercise, DLCO can improve, through an increase of capillary volume (Vc), that is blood volume participating to lung gases exchange. Previous observations show that also membrane diffusion (Dm), the other subcomponent of DLCO, can increase during effort. We hypothesized involvement of NO in vasodilatation of pulmonary capillaries (determining increase of Vc), but also in increasing permeability of alveolar-capillary membrane to gases (determining increase of Dm).

For this aim, we evaluated 20 patients affected by heart failure (19 males; age: 62.7 ± 9.2 years; ejection fraction: 33.8 ± 8.3%; NYHA class: 1.7 ± 0.7; Minnesota score: 27.5 ± 20.4), in stable clinical conditions. They underwent to respiratory function tests, maximal cardiopulmonary test and measurement, at rest and during submaximal constant workload exercise, of DLCO and exhaled NO. These results were compared with data of 10 normal subjects (10 males, age: 61.8 ± 6.7; Minnesota score: 5.6 ± 6.0). In HF patients DLCO (impaired at rest, 74.9 ± 17.6% of predicted value) significantly increases during effort, as Vc does. Baseline value of Vc and its increase during effort correlate with exercise induced increase of DLCO. NO values, both at rest and during effort, do not correlate with DLCO and its subcomponents changes, nor with peak VO2.

However a correlation (r = 0.379; p = 0.003) was found between NO and DLCO, when all values (controls and patients at rest and during effort) were considered. A similar correlation was also found between NO and DM values (r = 0.375; p = 0.004).

	HF Patients Rest	HF patients Exercise	Controls Rest	Controls Exercise
DLCO	20.0 ± 4.4	21.9 ± 4.9*	26.1 ± 4.4	27.6 ± 4.3*
Vc	92.0 ± 41.3	109.6 ± 41.0*	104.7 ± 26.6	113.0 ± 19.5
DM	31.5 ± 11.1	31.2 ± 9.1	39.9 ± 6.9	41.7 ± 10.0
NO	10.9 ± 5.5	10.4 ± 4.8	15.7 ± 5.6	13.3 ± 4.6*

* = p < 0.05

These data can support the hypothesis of an active role of NO in preserving DLCO and its physiological increase during effort.

P3650 Serum magnesium concentration tends to increase slightly in response to dosages of the loop diuretic torasemide that are used in heart failure

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Background: In the nephron, most filtered magnesium (Mg) is reabsorbed in the proximal tubule (PT) and in the loop of Henle (LH). Loop diuretics block reabsorptions in the LH and, with the exception of torasemide (T), also interfere with reabsorptions in the PT. Furosemide (Fur) increases magnesiuresis and usually reduces serum Mg concentration (SMg) in patients with heart failure (HF) and unimpaired renal function. The objective of this study was to evaluate formally the response of SMg to T.
Methods: Sixteen healthy subjects (age range: 19-26) in a metabolic unit took oral doses of placebo (Pla) and of T 2.5, 5 and 10 mg, at 08.00 hours once daily (od), during four separate single-treatment periods of 7 days each. The design was crossover, individually randomised and double-blind. Data are presented as mean ± SD.
Results: Just before and 1.5, 6 and 24 h after administration of Pla on day 1, SMg was 0.78 ± 0.04, 0.78 ± 0.05, 0.79 ± 0.04 and 0.80 ± 0.05 mmol/L; corresponding day-7 values, which did not differ from day-1 values (paired t test), were 0.77 ± 0.05, 0.78 ± 0.05, 0.79 ± 0.06 and 0.79 ± 0.06 mmol/L. Just before and 1.5, 6 and 24 h after dosing with 2.5 mg T on day 1, SMg was 0.77 ± 0.04, 0.78 ± 0.05, 0.79 ± 0.05 and 0.79 ± 0.04 mmol/L, and it was 0.80 ± 0.05, 0.78 ± 0.04, 0.79 ± 0.06 and 0.79 ± 0.04 mmol/L on day 7; corresponding day-7 and day-1 mean values did not differ. SMg was 0.78 ± 0.04, 0.77 ± 0.04, 0.75 ± 0.04 and 0.81 ± 0.05 mmol/L just before and 1.5, 6 and 24 h after dosing with 5 mg T on day 1; on day 7 it was 0.80 ± 0.03 ($p < 0.05$ vs. day 1), 0.77 ± 0.05, 0.80 ± 0.06 ($p < 0.01$ vs. day 1) and 0.82 ± 0.06 mmol/L. Just before and 1.5, 6 and 24 h after dosing with 10 mg T on day 1, SMg was 0.78 ± 0.06, 0.77 ± 0.06, 0.76 ± 0.05 and 0.81 ± 0.04 mmol/L; corresponding day-7 values were 0.82 ± 0.06 ($p < 0.01$ vs. day 1), 0.78 ± 0.05, 0.80 ± 0.05 ($p < 0.01$ vs. day 1) and 0.82 ± 0.05 mmol/L. At 08.00 hours on day 7, SMg was higher during treatment with T 10 mg than with Pla (ANOVA for repeated measures: $p < 0.01$; Dunnett's test: $p < 0.01$).
Conclusions: The small rises in SMg in response to T 5 and 10 mg od are consistent with a previous finding in patients with HF. In a similar study in healthy subjects, SMg fell after one week of treatment with 40 mg Fur od. All loop diuretics tend to elevate calciuresis and thus raise parathyroid hormone (PTH), which increases SMg. This rise in PTH could explain the small increase in SMg caused by T, given that T blocks Mg reabsorption in the LH but not in the PT. These results may well be of therapeutic importance.

P3651 Effects of the α1-adrenoceptor antagonist doxazosin on the cardiac index in patients with chronic congestive heart failure

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Background Nonselective alpha-adrenoceptor antagonists have not demonstrated significant beneficial effects in chronic heart failure. We examined the effects of the selective alpha1-adrenoceptor antagonist doxazosin on the cardiac index in patients with chronic congestive heart failure.
Methods Our double-blind, randomized trial was conducted on 30 patients with chronic congestive heart failure (NYHA III-IV), with cardiac index < 2.5 l/min x m^2, and/or with pulmonary capillary wedge pressure > 16 mmHg. We treated 15 patients with doxazosin and 15 with placebos, adjuvant to standard oral therapy, which included a minimum of an ACE inhibitor and a diuretic. Hemodynamic measurements were performed on days 1 and 2, and after 12 weeks on study medication. On day 1, patients were treated with 4 mg doxazosin versus placebo. On day 2 and the following 12 weeks, the patients were treated with 4 mg or 8 mg doxazosin/day (the latter, if 4 mg/day did not induce significant hemodynamic changes) versus placebo. Statistical analysis was performed using non-parametric rank variance analysis for longitudinal data. Differences between independent and dependent groups were determined by the Mann-Whitney U-test and the Wilcoxon test, respectively. Dichotomous variables were analyzed by the exact chi-square test.
Results Six patients were treated with 4 mg doxazosin/day, 9 patients with 8 mg doxazosin/day, and 15 with placebo. Baseline values for the cardiac index failed to disclose significant differences between patient groups and between the days of study. The maximum value for the cardiac index was 3.5 l/min x m^2 in the 4 mg doxazosin group, 2.6 l/min x m^2 in the 8 mg doxazosin group, and 2.6 l/min x m^2 in the placebo group. The increase in cardiac index compared to baseline was significantly higher in the 4 mg doxazosin group than in the placebo group ($p = 0.046$). Between the 8 mg doxazosin group and the placebo patients there was no significant difference ($p = 0.695$).
Conclusion Oral application of doxazosin supplementary to previous medication resulted in significant increase in cardiac index only in a minority of patients. Sixty percent of those receiving doxazosin were non-responders.

P3652 C-reactive protein predicts improved systolic performance in patients with idiopathic dilated cardiomyopathy treated with pentoxifylline

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Background: The acute phase protein C-reactive protein (CRP) was found to be elevated in acute cardiac decompensation and is associated with adverse prognosis in patients with idiopathic dilated cardiomyopathy (IDC). It is not known whether elevation of this inflammatory mediator at baseline can predict the response to Pentoxifylline (PTX; a drug known to modulate cytokines as TNF-alpha, IL-6, IL-10 and Fas/Apo-1).
Methods: In the present study, we combined the results of two prospective, randomised, double blind placebo-controlled trials in patients with IDC. In the 1st study, patients in the placebo arm were treated with diuretics, digoxin and ACE-inhibitors, and in the 2nd study carvedilol was added to this placebo therapy. The treatment arm in both studies received PTX 400 mg TDS in addition to the respective placebo therapy. Patients were treated for 6 months. Cardiac dimensions and function was determined by echocardiography and from radionuclide studies. TNF-alpha plasma concentrations were determined at baseline and after treatment. CRP was measured at baseline.
Results: There were no differences in baseline characteristics between the 45 patients in the treatment group and the 43 patients in the placebo arm. Thirteen patients died (9 in the placebo group, p=0.058 between groups). The PTX treated patients had a significant increase in ejection fraction (22.2±9% to 33.1±15%, $p<0.0001$) and a significant decline in the TNF-alpha plasma levels (7.5±5.6 pg/ml to 2.1±1.5 pg/ml) wheras no significant changes occurred in the placebo group.
Fifteen of the PTX treated patients improved their ejection fraction by more than 10 absolute units. These patients had a significantly higher CRP at baseline (14.2±6.2 mg/l) compared to the patients that did not improve on PTX (n=26; 7.2±4.5 mg/l;$p<0.0004$). There was a significant association between CRP>10 mg/l and TNF-alpha >5 pg/ml ($p<0.0005$).
Multiregression analysis showed that CRP >10 mg/l is an independent predictor of the ejection fraction after 6 months of therapy with PTX (r=0.30;p=0.039).
Conclusion: In patients with IDC, baseline levels of CRP may identify a group of patients with a better response to treatment with pentoxifylline.

P3653 Short-term haemodynamic effects of levosimendan versus prostaglandin E1 in refractory, decompensated chronic heart failure patients

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Background: We compared the hemodynamic effect of 24 hours infusion of the balanced vasodilator prostaglandin E1 (PGE1) with the inodilator levosimendan in refractory, decompensated chronic heart failure patients.
Methods: 17 patients (LVEF <25%) in NYHA class IV despite optimized therapy with high dose RAAS antagonists (100%), beta-blockade (82%) and furosemide (mean dose 74±49 mg/day) were randomized to low dose 24 hours PGE1-infusion (low dose: 2,5 ng/kg/min.; n=8) or levosimendan (10 minutes bolus: 12 µg/kg/min. followed by 0,1 µg/kg/min.; n=9). Hemodynamic evaluation with right heart catheterization was performed at baseline and after 24 hours.
Results: At baseline, mean values of heart rate (69±13/min.), RR mean (73±14 mmHg), CVD (10±6 mmHg), PAP mean (35±9 mmHg), PCWP (24±6 mmHg), CI (1,7±0,2 l/min.m^2), SVR (1527±406 dyn.sec/cm5) and PVR (267±131 dyn.sec/cm5) were comparable in both groups. After 24 hours, patients with levosimendan showed a significant decrease of PAP mean (from 37±9 to 32±6; p=0.03) and PCWP (from 25±6 to 21±6; p=0.05) and a significant increase of CI (from 1,7±0,3 to 2,2±0,6; p=0.0005) resulting in a significant decrease of SVR (from 1374±354 to 1071±287; p=0.03). Patients treated with PGE1 showed a significant decrease of PAP mean (from 33±9 to 30±8; p=0.03) and PCWP (from 22±5 to 18±4; p=0.02).
Conclusion: 24 hours infusion with both drugs resulted in a comparable, significant decrease of PAP mean and PCWP. Only levosimendan significantly increases CI resulting in a significant decrease of SVR.

P3654 Short-term effects of levosimendan versus prostaglandin E1 on haemodynamics and BNP plasma levels in patients with chronic heart failure

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Background: The balanced vasodilator prostaglandin E1 (PGE1) as well as the calcium sensitizer levosimendan are used for treatment of patients with refractory, decompensated chronic heart failure. We compared the effects of a 24 hours infusion with levosimendan and PGE1 on hemodynamics and BNP plasma levels in these patients. **Methods:** 24 patients (LVEF<25%) in NYHA class IV despite optimised therapy with RAAS antagonists (100%), beta-blockers (83%) and furosemide (72 ± 50 mg/day) were randomised to a 24 hours infusion with levosimendan (10 minutes bolus with 12 μg/kg/min followed by 0.1 μg/kg/min) or with low-dose (2.5 ng/kg/min) PGE1. Evaluation of hemodynamics with right heart catheterisation and of BNP plasma levels were performed at baseline and after 24 and 48 hours. **Results:** At baseline, mean values of heart rate (68±12/min), RRmean (73±12 mmHg), CVP (10±6 mmHg), PAPmean (36±9 mmHg), PCP (23±5 mmHg), CI (1.8±0.3l/min m^2), SVR (1458±384 dyn sec/cm^5), PVR (285±140 dyn sec/cm^5) and BNP levels (740±612 pg/ml) were comparable between groups. After 24 hours, patients with levosimendan (n=14) showed a significant decrease of RRmean (from 70±7 to 66±9; p=0.04), PAPmean (from 37±9 to 33±7; p=0.003) and PCP (from 24±5 to 20±5; p=0.008) and a significant increase of CI (from 1.8±0.4 to 2.2±0.6; p=0.004) resulting in a significant decrease of SVR (from 1364±331 to 1076±269; p=0.01). BNP levels decreased from 833±739 to 569±469 (p=0.01). Patients treated with PGE1 (n=10) showed a significant decrease of CVP (from 8±4 to 6±3; p=0.02), PAPmean (34±8 to 30±7; p=0.02) and PCP (from 22±4 to 18±4; p=0.003). **Conclusion:** 24 hours infusion with both drugs resulted in a comparable, significant decrease of PAPmean and PCP. Only levosimendan significantly increased CI (resulting in a significant decrease of SVR) and significantly decreased BNP plasma levels.

P3655 The impact of intermittent intravenous dobutamine therapy on endothelial function in patients with severe chronic heart failure

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Background: Intermittent intravenous (i.v.) dobutamine therapy is used to treat decompensated end-stage heart failure patients. However, its use has not been adequately documented in controlled trials and its prognostic effects are not well delineated. Chronic heart failure (CHF) is associated with abnormal endothelium-dependent vasodilation. The impact of short-term i.v. dobutamine on flow-mediated dilation (FMD) has not yet been assessed. **Methods:** We prospectively assessed intermittent i.v. dobutamine therapy (up to dose 5 mcg/kg/min), endothelium-dependent brachial artery FMD and endothelium-independent nitroglycerin-mediated vasodilation (NTG) using high resolution (16 MHz) ultrasound in 15 consecutive severe CHF male patients (New York Heart association class III-IV) (mean age 57±11 years, mean left ventricular ejection fraction 22±8%), at baseline and after 3-4 months. Cardiac index (CI), stroke index (SI), and systemic vascular resistance (SVR) were assessed non-invasively by bio-impedance technique, prior to and post i.v. dobutamine therapy. **Results:** (see table). All patients had ischemic cardiomyopathy. 61% of severe CHF patients received aspirin, long-acting nitrates, and beta blockers, 83% angiotensine converting-enzyme inhibitors, 5% calcium blockers, 56% spirinolactone, 44% statins, digoxin, and coumadin, and 33% multivitamins.

	%FMD	%NTG	SVR (dyne sec/cm^2)	CI (l/min/m^2)	SI (ml/m^2)
Baseline	1.1±5.3	7.5±8.8	2172±1133	1.9±0.6	27.2±12.4
Post therapy	7.7±4.6	7.6±5.5	1797±926	2.4±0.6	33.5±11.7
p-value	0.001	0.979	0.05	0.016	0.024

Values are expressed as mean±SD; %FMD, %NTG=%change from baseline in brachial artery diameter caused by FMD and NTG, respectively.

Conclusion: Severe CHF patients suffer from impaired endothelium-dependent and -independent vasodilation, suggesting the presence of both endothelial and smooth muscle dysfunction. Short-term intermittent i.v. dobutamine therapy, however, can significantly improve vascular endothelial function, perhaps demonstrating an additional mechanism whereby SVR, CI and SI are improved in severe CHF patients treated by i.v. dobutamine.

P3656 Gradual reactivation over time of vascular tissue angiotensin I to angiotensin II conversion despite angiotensin-converting enzyme inhibition therapy in chronic heart failure

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Background: Plasma angiotensin II does not remain fully suppressed during chronic ACEI therapy in chronic heart failure (CHF). However, evidence suggests that the plasma renin angiotensin system (RAS) might be dissociated from the vascular tissue RAS. We therefore set out to characterise for the first time in vivo in man the time course of vascular RAS reactivation during chronic ACEI therapy.
Methods: Vascular AI/AII conversion was studied in CHF patients taking chronic lisinopril therapy. In a cross sectional study, 37 patients with NYHA Class I-III CHF were studied to see whether there were differences in vascular AI/AII conversion according to NYHA Class. A second longitudinal study followed 28 patients with NYHA I-II CHF serially over 18 months to see whether vascular ACE inhibition was progressively lost with time despite ACEI therapy. A third study took patients with the least vascular ACE inhibition observed in the first study to see whether increasing the dose of lisinopril in a double-blind cross-over fashion affected subsequent vascular ACE inhibition.
Results: In the cross sectional study, vascular ACE inhibition was significantly reduced in NYHA Class III compared with Class I/II ($p<0.05$), suggesting that tissue inhibition is more difficult to achieve with standard doses of ACEI in more severe CHF. In the longitudinal study, vascular ACE inhibition was significantly reduced at 18 months as compared with baseline ($p<0.001$), suggesting reactivation of vascular ACE in CHF despite initially achieving satisfactory ACE inhibition. In the third study, tissue ACE inhibition could once again be restored by increasing the ACEI dose compared with baseline ($p<0.001$), suggesting that this reactivation of vascular AI/AII conversion is at least partly ACE-dependent. In all studies, neither plasma angiotensin II levels, plasma aldosterone or plasma angiotensin II/I ratios bore any correlation with vascular responses, consistent with dissocation between plasma and tissue-bound ACE systems.
Conclusions: Vascular AI/AII conversion reactivates over time during chronic ACEI therapy. This occurs over time even if the CHF disease process is apparently clinically stable. It also occurs as the CHF disease process progresses. Even if vascular AI/AII conversion has reactivated, it can be suppressed by increasing the dose of the ACE inhibitor. There is no correlation whatever between any plasma RAS markers and vascular tissue AI/AII conversion.

P3657 What is the relation between drug therapy and survival in real world heart failure patients?

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Background and Aims: Evidence from randomized clinical trials forms the basis for heart failure (HF) treatment guidelines but trial data are collected in carefully selected pts who meet strict inclusion/exclusion criteria. We examined drug therapy and 12 mth survival in a real world HF population. **Patients and Methods:** Drug therapy was recorded during index admission in 362 consecutive pts hospitalized for HF or suspected HF (drug treatment compatible with HF/LV dysfunction) and enrolled on discharge into the European Heart Failure survey. Survival status was ascertained for all pts by telephone interview and/or governmental records. **Results:** Drug therapy included digoxin in 97 (27.6%) pts, diuretics in 325 (92.6%), ACE-inhibitors in 234 (66.7%), angiotensin receptor blockers in 21 (6.0%) and beta blockers in 142 (40.5%). In addition, nitrates were given to 186 (53.0%) pts, calcium antagonists to 96 (27.4%), anti-thrombotic drugs (aspirin/heparin/warfarin) to 283 (80.6%) and anti-arrhythmics to 67 (19.1%) pts. At one year, 90/362 (25%) of the pts had died. Mortality was lower by 36% in pts receiving ACE-inhibitor (24.8% vs 38.5%, p=0.008), by 42% with beta blocker (20.4% vs 35.4%, p=0.002) and by 32% with anti-thrombotic therapy (26.9% vs 39.7%, p=0.037). There was no difference in mortality in pts receiving diuretics (29.8% vs 23.1%, NS), nitroglycerin (26.3% vs 32.7%, NS) and anti-arrhythmic drugs (28.4% vs 29.6%, NS). **Conclusions:** In a consecutive population of pts hospitalized for HF: 1. 12 mth mortality was lower in pts treated with ACE-inhibitors (-36%), beta blockers (-42%) and anti-thrombotic drugs (-32%). 2. Use of digoxin, diuretics and calcium antagonists had no relation to 12 mth mortality. 3. The findings were in keeping with results of major clinical trials and strongly support applicability of treatment guidelines to the real world HF population.

Abstract P3657 – Table: Drug therapy and 12 mth survival

	Digoxin		Diuretic		ACE-inhibitor		Beta blocker		Ca antagonist	
	yes	no	yes	no	yes	no	yes	no	yes	no
dead	29 (29.9%)	74 (29.1%)	97 (29.8%)	6 (23.1%)	58 (24.8%)	45 (38.5%)	29 (20.4%)	74 (35.4%)	28 (29.2%)	75 (29.4%)
alive	68 (70.1%)	180 (70.9%)	228 (70.2%)	20 (76.9%)	176 (75.2%)	72 (61.5%)	113 (79.6%)	135 (64.6%)	68 (70.8%)	180 (70.6%)
p value	0.88		0.46		0.008		0.002		0.96	

12 mth survival was higher in pts receiving ACE-inhibitor and beta blocker

P3658 Continuous positive airway pressure by "helmet" in acute pulmonary oedema. Report of 60 cases

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Background: Acute cardiogenic pulmonary edema (ACPE) is a frequent cause of respiratory failure. Positive pressure ventilation had been shown to be more effective than conventional pharmacologic treatment by several studies in the literature. Its use was associated with the reduction of number of orotracheal intubations and costs. The aim of our study is to show the efficacy, safety and feasibility of an alternative cPAP (continuous positive airway pressure) system in patients with cardiogenic pulmonary edema admitted to a Coronary Care Unit (CCU).
Methods: Retrospective analysis of clinical reports of 60 consecutive patients with ACPE treated with helmet cPAP admitted in CCU during 10 mounths in 2001. The helmet c-PAP (Plain Hood & Neckseal SEA-LONG Medical System Inc. Horsham, UK) is a non-invasive system with the shape of a cylinder with a PVC transparent upper part and a latex lower one which fits around the patient's neck. It is equiped with an inspiratory limb connected to a flow meter and expiratory valve that allows the maintenance of a positive pressure.
Results: Non-invasive cPAP improved blood pressure (BP), heart rate (HR), rate-pressure product and blood gas parameters. The average values of HR have decreased from 105±29 mmHg to 94±25 in one hour ($p<0.001$) and to 83±16 after 9hrs ($p<0.001$); systolic blood pressure from 148±39 to 127±21 in 1h ($p<0.001$); diastolic blood pressure from 83±23 to 72±12 in 1h ($p<0.001$). In the time interval of 1 hour PaO2 improved from 66±25 mmHg to 220±115 ($p<0.001$), pCO2 from 46±16 mmHg to 39±6 mmHg after 9hrs ($p<0.001$), arterial saturation of O2 from 86%±10% to 98%±2 in 1hour ($p<0.001$), the PaO2/FiO2 ratio from 118±67 to 241±119 ($p<0.001$), arterial pH from 7.27±0.1 to 7.34±0.09 in 1 hour ($p<0.001$) and to 7.42±0.07 after 9hrs ($p<0.001$). 12% of patients died during c-PAP treatment. The 7.1% of the patients were intubated and ventilated. The records analyzed revealed intolerance of the method in only 1 patient after one hour of treatment. No complications were observed.
Conclusions: "Helmet" cPAP is an effective tool for ACPE treatment and is easily applicable. It rapidly improves oxygenation and is associated with improvement of hemodynamic parameters.
Comments: Although helmet cPAP is used in ACPE treatment in many hospitals in Italy, the studies in literature suppporting the use of cPAP in ACPE are all made with the tight fitting mask. There aren't in literature studies describing "helmet" efficacy and applicability. Our work is the first official documentation.

STROKE

P3659 Efficacy and problems in transcatheter closure of patent foramen ovale in patients with cryptogenic cerebrovascular events

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The role of the patent foramen ovale (PFO) in patients with cryptogenic cerebrovascular events is well documented. By transesophageal echocardiography (TEE)incidence of a PFO with right to left shunting, its size and shape as well as additional atrial septal aneurysm formation in those patients can be defined. Transcatheter closure being the widely used alternative treatment to drug therapy or surgery also has its problems.
In 228 adult patients (aged 18 to 71 years) with a history of at least one cryptogenic cerebrovascular event (64% stroke, 46% TIA or PRIND)TEE proved a PFO and transcatheter closure was performed. During the procedure TEE was used in the majority of patients to define the shape of the PFO and atrial septum and detect other abnormalities or additional defects. TEE findings and balloonsizing determined the type and size of the device used. For anticoagulation heparine was given for 24 h around the procedure, antiplatelet therapy for the following 6 months. We successfully implanted 109 Amplatzer PFO occluders (APFO),76 Cardioseal(CS) and 36 CS-Starflex (CSStf) devices. The vast majority of the APFO were 25 mm devices. In the CS/CSStf group more than 2/3 were 23mm and 28mm. In large ASA or PFO >10mm 33 or 40mm devices were used.
There were early complications like device embolization due to inappropriate size of the device (CS 2) and early release.Devices could be removed from the femoral groin. Undetected perforation of the roof of the left atrium with the guide wire lead to cardiac tamponade and surgery 6 hours after successfull implantation of a device.In five patients significant venous hematoma occurred. As late complications there was 1 LA-perforation by the leftatrial disc of a APFO with the need of urgent surgery. Late arrhythmias(atrial flutter, fibrillation)with shortterm therapy occurred in 5%. Residual leaks and/or an additional lesion detected on TEE after 6 months were trivial in 3, 4 others have got a second device.
These different devices we report are the mainly used for closing a PFO.Problems may occur with the larger sized CS/CSSTf used in long tunnel-like PFOs with late dislocation after immediate correct positioning, or infolding of the device into the tunnel and incomplete contact with the septum. APFO-devices are more bulky and we had 1 late perforation. Transcatheter closure of a PFO is effective in terms of closure rate, is preferable to longtime anticoagulation or other drug therapy, and its recurrance rate of neurological events is low.

P3660 Percutaneous closure of patent foramen ovale in young adults with cerebral infarction – Results with the CardioSeal Starflex Occluder

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Background: Prevalence of patent foramen ovale (PFO) with detectable right-to-left shunt is high in young adults with TIA/cerebral infarction and is associated with increased risk for recurrent paradoxical thrombembolism. Percutaneous closure represents a promising therapeutic concept since it avoids surgical closure or life-long anticoagulation with coumadin. So far, however, published data included different occluder systems, different indications (PFO with small/large shunt; ASD II) and different regimens of anticoagulation after the procedure within the same study.
Methods and Results: Accordingly, in the present study 51 young adults (27 men; age: 43±2 years) with >1 TIA/stroke documented by CCT or MRI were included. All had PFO with large right to left shunt (Valsalva: >50% of left atrium filled with contrast during TEE) and/or PFO with atrial septum aneurysm, since it has recently been demonstrated that particularly these conditions are associated with increased risk of recurrent stroke. Other sources of embolism were excluded. Implantation of the CardioSeal Starflex Occluder was performed under local anaesthesia, fluoroscopic and TEE guidance (procedure including diagnostic right and left heart catheterization: time 52±2 min, contrast medium 45±2 ml, fluoroscopy time 5.4±0.5 min). PFO-closure was successfull in 50 patients (98.0%). All patients were subsequently treated for 6 months with Phenprocoumon (INR 2.5) to inhibit plasmatic coagulation and Aspirin (100mg/d) to inhibit thrombocyte aggregation. Follow-up included contrast-enriched TEE with Valsalva manoeuvre after 6 months and a health questionnaire every 6 months. After 6 months PFO was completely occluded in 92% of the patients, in 3 cases a residual shunt (small) was detected. None of the patients had local thrombus formation on the occluder system. The mean follow-up with the health questionnaire is 15.4±6.6 months (range 6 to 28 months) and revealed recurrent neurological symptoms in 4 patients with completely occluded PFO. In 2 of these cases symptoms were associated with migraine and in the other 2 cases a cerebral infarction was excluded by NMR. All other patients (92%) were free of recurrent neurological events. Six patients developed supraventricular arrhythmias which needed no treatment (n=4) or were successfuly treated with b-blockers (n=2).
Conclusion: Percutaneous closure of patent foramen ovale with the CardioSeal Starflex Occluder represents a safe and effective therapy for appropriately selected young adults to prevent recurrent cerebral ischemic events.

P3661 The impact of physical activity on stroke mortality, in elderly individuals: forty-years follow-up of the Corfu cohort; Seven Countries study

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Background: Stroke is one of the leading causes of death, universally. This analysis aims at describing the effects of physical activity on the stroke mortality, based on 40-years (1961-2001) prospective evaluation of the Corfu cohort, from the Seven Countries Study. **Methods:** The population studied in this analysis consisted of rural men enrolled at 1961 (n=529, 49.7±5.7 years old) in Corfu. Among several factors the effect of moderate or vigorous physical exercise was evaluated with stroke mortality as the end-point. Cox proportional hazards models were applied in order to evaluate the investigated parameters. A major limitation of the study was our inability to segregate thrombotic from hemorrhagic strokes. **Results:** Among 529 cardiovascular disease-free men at entry, 65 (12.3%) died because of cerebrovascular disease. The cumulative survival at the end of the follow-up was 76%. Mean age at death for stroke was 75 ± 9 years old. At baseline, 167 (32%) reported sedentary life, 197 (36%) moderated exercise and the rest of them 165 (31%) reported vigorous physical activity. Compared to subjects reported sedentary life at baseline, those reported moderate physical exercise had 42% (hazard ratio = 0.58, $p < 0.01$) lower risk of fatal stroke evens, while those reported vigorous exercise had 35% (hazard ratio = 0.65, $p < 0.05$) lower risk, after adjusting for arterial blood pressure, smoking habits and body mass index. **Conclusions:** In these elderly men 40-years incidence of cerebrovascular disease seems to be strongly associated with the presence of physical activity, at baseline. The effect of physical activity on stroke mortality, was independent from arterial blood pressure levels, body mass and smoking habits.

P3662 Carotid angioplasty: initial experience with the flow reversal technique for prevention of embolic complications

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Background: Complications of carotid angioplasty usually occur due to embolization of arteriosclerotic debris. Reversal of blood flow in the internal carotid artery during angioplasty and stenting has been suggested to prevent this. **Patients:** Carotid angioplasty and stenting under flow reversal was attempted in 34 patients (age 68 ± 9). 16 patients had a previous ipsilateral TIA and or stroke. Diameter stenosis ranged from 60 to 99,9% (79 ± 10), the length of the lesion ranged from 1 to 24,6 mm. At least 4 lesions contained fresh thrombus. Two patients had a contralateral stenosis of > 50% and one patient had a contralateral occlusion. **Methods:** Reversal of blood flow in the internal carotid artery was achieved by occlusion of both the common and the external carotid artery during the procedure using the ArteriaO device. During the procedure the blood flowing back into the guiding catheter was re-transfused into the femoral vein via a filter. Conventional wires and balloons where used. A Wall-Stent was implanted in 24 patients. 7 patients received a Precise-Stent, 2 patients a Smart-Stent and 1 patient a Tetra-Stent. **Results:** The device could easily be introduced into the common carotid artery. Balloon occlusion of the common carotid artery as well as the external carotid artery was achieved in all patients. The occlusion time ranged between 4 and 37 min (15 ± 8) and was tolerated reasonable in all patients except one, in whom the balloon had to be deflated repeatedly during the procedure. Two patients experienced transient neurological symptoms during balloon occlusion without need for interruption of the procedure. In all patients angiographic success was achieved without immediate complications. In one patient a TIA occurred several hours later. Macroscopic debris was found in the filter in 32/34 patients. **Conclusions:** Flow reversal in the carotid artery for protection of embolism during carotid angioplasty is feasible in the majority of patients. Atherosclerotic debris is kept back efficiently. If the balloon occlusion is not tolerated, the procedure can be completed by deflating the balloon intermittently. As in any other embolic protection device, late ischemic events can not be avoided.

P3663 Galantamine is effective for at least 12 months in patients with vascular dementia and Alzheimer's diesase with cerebrovascular disease

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Background: Large artery disease, small vessel disease, cardiac embolic phenomena and hemodynamic mechanisms are all frequent etiologies associated with cerebrovascular disease (CVD) and subsequent dementia. Various cardiovascular risk factors such as hypertension, atherosclerosis, diabetes mellitus and hyperlipidemia are also thought to contribute. To date, the treatment of dementia related to CVD has focused on primary prevention of some of these risk factors. However, galantamine (Reminyl®), a cholinergic dementia treatment with a novel dual mode of action, has recently shown broad, significant benefits for up to 6 months in patients with vascular dementia (VaD) and Alzheimer's disease (AD) with CVD. Galantamine is the first cholinergic agent to demonstrate such efficacy in these patient groups. Here we report further data on the long-term (12-month) maintenance of cognitive function from a 6-month open-label extension to the initial 6-month double-blind study.
Methods: Patients with VaD or AD+CVD who had completed a 6-month, randomized, double-blind trial with galantamine 24 mg/day or placebo were eligible to enter a 6-month, open-label extension study. All patients in the open-label study received galantamine 24 mg/day up to Month 12, irrespective of whether they had received placebo or galantamine during the double-blind phase. Cognitive function was measured at baseline and at Months 6, 7.5 and 12 (endpoint) using the 11-item Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog/11).
Results: Overall, 459 patients received open-label treatment with galantamine; 195 (42%) had probable VaD. 73% of placebo/galantamine and 86% of galantamine/galantamine patients completed 6 months of open-label treatment. At the end of 6 months of double-blind treatment, ADAS-cog/11 scores had significantly improved over baseline in the galantamine group ($p < 0.001$). After a further 6 months of galantamine (12-months' follow-up), ADAS-cog/11 scores were still better than baseline (-0.9 ± 0.45), but not significantly so. Placebo patients had deteriorated significantly during the double-blind phase, but their ADAS-cog/11 scores returned to baseline after 6 months of open-label galantamine (-0.3 ± 0.68).
Conclusion: The maintenance of cognitive function at baseline levels for at least 12 months represents an important clinical benefit in patients with probable VaD or AD+CVD. This 12-month, open-label extension study with galantamine represents the first robust evidence for such efficacy with a cholinergic agent in these patient groups.

P3664 The – 174 g/c polymorphism of the il-6 gene promoter is associated with multi-infarct dementia in an Italian population

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Introduction: Multi-Infarct Dementia (MID) is a pathology whose incidence has greatly increased over the last decades. Recently, attention has been paid to the role of inflammatory processes in the progression of cerebrovascular diseases. Several observations hint at the role of inflammatory mechanisms in the development, maturation and destabilization of atherosclerotic plaque. Pro-inflammatory cytokines have been localized into the atherosclerotic vessel wall, and there is evidence that this profile shifts the endothelium towards a prothrombotic state. In addition, an increment of pro-inflammatory mediators, such as TNF-alpha, IL-6, and IL-8, has been observed in ischemic cerebral areas. These data are consistent with the observation that elevated levels of IL-6 in plasma increase the risk of future myocardial infarction in an apparently healthy population. A common genetic polymorphism has been reported in the promoter region of the IL-6 gene. This polymorphism is functionally important, since it influences the transcription rate of the gene. Two different alleles of the IL-6 gene can be identified (G and C allele), resulting in three possible genotypes, GG, GC, and CC. Recently, this polymorphism has been associated with intima-media thickness and abdominal aortic aneurysms.
Methods: the IL-6 G/C gene polymorphism was analyzed in 122 patients with MID and 134 age- and sex-matched controls. All subjects were Caucasians from central and southern Italy.
Results: The distribution of IL-6 genotypes in MID patients was 63 GG, 47 GC, 12 CC, and differed significantly from that observed in the 134 control subjects: 29 GG, 58 GC, 47 CC. The GG genotype was significantly more common in patients with MID than in the control group ($P<0.0001$), while the CC genotype was significantly more frequent in control subjects ($P<0.0001$). The GC genotype was not significantly different between the 2 groups ($P=0.432$). The allele distribution was significantly different between the two groups, as well ($P<0.0001$). A linear regression analysis demonstrated that GG genotype is an independent risk factor for MID: Odds ratio for the GG genotype was 9.1 (3.1-26.1), $P<0.0001$.
Conclusions: In this study, we provide evidence that the -174 G/C polymorphism of the IL-6 gene promoter is a risk factor for MID in an Italian population. Although further studies are needed, our data support the hypothesis that IL-6 is important in the pathophysiology of cerebrovascular disorders and suggest a role for anti-inflammatory therapy in these diseases.

LEFT VENTRICLE AFTER INFARCTION: REMODELLING, PERFUSION, FUNCTION

P3665 Correlation of pacing "Stress" NOGA with angiography for the detection of myocardium ischaemia

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Introduction: Electromechanical maps (EMM)have been shown to accurately detect chronic severe myocardial ischemia (hybernating myocardium).Linear Local shortening(LLS) function is utilized to assess myocardial contractility.The present study investigates if a "stress" mode of EMM can enhance the detection of myocardial ischemia when compared to the "gold standard" coronary angiography.
Methods: In 22 patients with proven myocardial ischemia by SPECT, coronary angiography was performed as well as rest and paced (85% MPHR) EMM. EMM were divided into five segments according to the regional distribution of the main epicardial coronary arteries(LAD:(1)Anterior-basal,(2)Mid-anterior,(3)apical; RCA:(4)Inferior; LCX:(5)Lateral). Of a total of 110 myocardial 87 were submitted to analysis. Twenty three were excluded because of the presence of scar or resting ischemia. Coronary lesions were measured using QCA and segments were divided in two groups:a)Group I: supplied by a vessel with <50% stenosis(n=44). b)Group II >= 50% stenosis(n=43). LLS(%)values (mean±SD) were obtained for both groups at rest and stress. An LLS "stress" index (LLS stress/LLS rest - 1) reflecting the mechanical response of each group to stress was calculated. A T-test was used to compare indexes. A $p<0.05$ was considered significant.
Results (see table): Using a LLS "stress" index of -0.40 as a threshold for diagnosis of myocardial ischemia EMM showed a specificity of 69.1% and sensitivity of 68.2%.

LLS at rest and with pacing

	Stenosis <50%	Stenosis >= 50%	P value
Rest LLS (%)	14.60 ± 7.40	13.60 ± 5.41	NS
Paced LLS (%)	12.6 ± 6.27	6.52 ± 4.63	<0.001
LLS Index	-0.04 ± 0.68	-0.49 ± 0.37	<0.001

LLS= linear local shortening

Conclusion: Pacing "stress" EMM is capable of detecting myocardial ischemia in non-hybernating and non-scarred myocardial segments.Its low sensitivity and specificity might limit it's use in clinical practice though future studies with larger sample sizes are needed to further address this matter.

P3666 Contrast echocardiography and its relationship with the intensity of the inflammatory response in the acute phase of myocardial infarction

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Myocardial ischemia, necrosis and rupture of the coronary microcirculation are directly related with the intensity of the inflammatory process that occurs during an acute myocardial infarction (AMI). Purpose: The aim of this study was to evaluate the relationship between the intensity of AMI inflammatory response and the extension of the left ventricular (LV) myocardial contrast enhancement (MCE) distribution. Methods: We studied a group of 26 patients with clinical, EKG and laboratorial AMI diagnosis. Between day 1 and 3 post AMI we calculated the mean (Mn) and maximal (Max) values of several laboratorial parameters, such as the C-reactive protein (CRP-U/L), troponin I (TI-U/L) and mioglobin (MG-U/L) levels, and CD11b, CD43, and its CD11b/CD43 ratio, cell adhesion molecule ligands to circulating monocytes (M). The MCE study was performed using intermittent imaging acquisition, 1:4 cardiac cycles, PCI software (Acuson, Mountain View, CI, USA), Doppler angio mode, after intravenous injection of MCE Levovist® (Schering AG, Germany) 4g/300 mg/ml, following the transthoracic echocardiographic ASE model of 16 LV myocardial segments. Computerized ultrasound densitometry was applied and its Max and Mn LV segmental myocardial wall intensity (UI-dB) values were calculated. The individual (Ind) and Mn LV segmental values of UI (dB) and its percentage (UI%-%) variation post MCE administration were used as quantitation parameters of LV MCE intra-myocardial distribution and change. LV wall segments wre divided in two groups according to the AMI related coronary artery. Results: For AMI related LV segments, an inverse correlation was observed between CRP Max and Mn values and the Mn and Ind values of UI (r=-0.37 and r=-0.42; p=0.03) and %UI (r=-0.44 and r=-0.46; p=0.02). Significant correlations were also obtained between CD11b/CD43 ratio and the UI Mn value (r=-0.47; p=0.01) and %UI (r=-0.45; p=0.02) of LV MCE study. No significant correlation was found for the LV mycardial wall segments not related with the AMI coronary artery lesion. Conclusion: In our population, the intensity of the inflammatory cell response to AMI is directly related with the reduction of the intra-myocardial distribution of MCE in the coronary involved segments during the first days post acute coronary event.

P3667 Serial echocardiographic assessment of the left ventricle function after the direct PTCA; a one-year follow-up

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Acute myocardial infarction (AMI) causes remodeling of the left ventricle (LV).
Aim of the study: Echocardiographic follow-up of the late LV remodeling in patients with acute myocardial infarction, who were treated with the direct percutaneous transluminal coronary angioplasty (PTCA). The patients were followed up from the discharge from the hospital for 12 months.
Methods: 61 patients with acute myocardial infarction treated with direct PTCA were included in the study. 47 were men and 14 women with average age 60 ± 10 years. Complete closure of the infarction-related coronary artery (TIMI flow 0) prior to the direct PTCA performance was diagnosed in 84% of the cases. Full patency of the artery (TIMI III) after the direct PTCA performance was diagnosed in 93% of the cases. An echocardiographic examination was performed on the 6th to 8th day after direct PTCA, at the end of the 1st month and after 6 and 12 months. We used a 16-segment model of the left ventricle. The ventricular wall motion was scored using a 4-grade scale (1 = normokinesis, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis). Ejection fraction (EF) was calculated by Simpson's method.
Results: The EF value increased significantly at the end of the first month in comparison with the examination performed on the 6th to 8th day after the direct PTCA increase from 46 ± 8% to 49 ± 8%, p = 0.005). The changes in EF after 6 months (EF = 50 ± 9%) and after 1 year (EF = 49 ± 7%) were not statistically significant.
The wall motion score index (WMSI) showed a statistically significant improvement after 1 month (1.64 ± 0.34 in the first examination, 1.53 ± 0.30 after 1 month, p = 0.004). The WMSI after 6 months (1.50 ± 0.32) and after 1 year (1.54 ± 0.28) did not show further statistically significant development. End-diastolic diameter (EDD)in the first examination on the 6th to 8th day after the direct PTCA was 49 ± 6mm. EDD did not change after one month, increased insignificantly to 50 ± 7 mm after 6 months and increased significantly to 51 ± 5mm after one year ($p < 0.05$).
Conclusion: The ejection fraction and the ventricular wall motion showed significant improvement in the period between one week and one month after the direct PTCA. The LV end-diastolic diameter showed only a small increase during the whole one-year follow-up. These results confirm the beneficial effects of achieving the infarct-related artery patency with direct PTCA on the LV remodeling after the AMI.

P3668 A mitral pattern of impaired relaxation and the presence of infarct-zone viability identify patients without left ventricular remodelling

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Acute myocardial infarction (AMI) is followed by a complex and interrelated sequence of events termed postinfarction left ventricular remodelling (LVR) which lead to heart failure and increased mortality. However LVR does not always occur, consequently some patients (pts) can not develop such an unfavourable eventuality. The aim of this study was to examine a group of pts with first AMI to evaluate if echocardiography parameters, at rest and during dobutamine stimulation, would be able to predict the absence of LVR.

Methods: 70 pts. with a first uncomplicated AMI (M=61, F=9), underwent complete 2-dimensional and Doppler echocardiographic examinations at predischarge and 6 months after the index infarction. End-diastolic left ventricular volume index (EDVI, mL/m^2) and end-systolic left ventricular volume index (ESVI, mL/m^2) were calculated by modified biplane Simpson's rule. From Doppler spectra of 3 consecutive cardiac cycles, averages values were calculated for the following diastolic variables: peak flow velocity of E (E) and A wave (A),peak E/A wave velocity ratio (E/A), deceleration time of early filling (Edt). Echo-dobutamine stress test to identify infarct-zone viability was performed at incremental doses (5 to 20 μg/Kg/min) in 3 min-steps. Infarct-zone viability was defined as any contractile improvement in > 2 left ventricular (LV) dysfunctioning segments during dobutamine stimulation, using standard 16-segments model of the LV and a 1-4 scoring system. Finally on the basis of LV dimension at 6 months, pts were divided in two subsets: those without (27 pts, Group 1) and those with (43 pts, Group 2) LV dilatation.

Results: Clinical characteristics and LV volume indexes (EDVI: 60 ± 12 Group 1 vs 65 ± 16 mL/m^2 Group 2, p = ns; ESVI: 34 ± 11 Group 1 vs 37 ± 11 mL/m^2 Group 2, p = ns, respectively) were similar in both groups at baseline. Group 2 had significantly greater end diastolic (77 ± 17 vs 57 ± 13 mL/m^2, p<0,0001) and end systolic (43 ± 13 vs 29 ± 9 mL/m^2, p<0,0001) volumes at 6 months than did patients in Group 1. Viable myocardium was found in 13 pts. of the Group 2 and in 17 pts.of the Group 1 (19% vs 62%, p<0,01), moreover Group 1 exhibited a mitral pattern of impaired relaxation, Group 2 a normal or rather pseudonormalized mitral pattern (E/A: 0,9 ± 0,3 vs 1,23 ± 0,4, p< 0,0001).

Conclusions: These data suggest that the presence of a residual infarct-zone viability and a mitral pattern of impaired relaxation discriminate patients who maintain left ventricular geometry from those who develop progressive LV dilatation after a first AMI.

P3669 Regional curvature and wall-motion abnormalities in anterior postinfarction cardiomyopathy with functional mitral regurgitation

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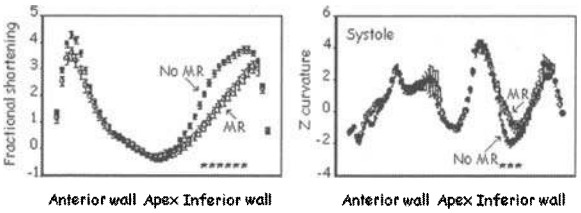
Several mechanisms were proposed for ischemic mitral regurgitation (IMR), including global left ventricular (LV) dysfunction, geometric distortion by LV dilatation, or regional segmental wall motion abnormalities. However, ventricular shape in IMR has not been fully elucidated.

LV shape in IMR has not been fully elucidated. The relationship between LV shape (eccentricity index -EI- and regional curvature analysis) and IMR was evaluated in 221 consecutive patients with anterior post-infarction scar submitted to diagnostic heart catheterization; 174 patients (60±9yrs) did not have and 47 (61±9yrs) had angiographic grade 2 MR or more.

In patients with IMR hemodynamics were significantly worse (EDVI 242±73 vs. 190±70 ml/m^2; ESVI 174±73 vs. 120±57 ml/m^2; EF 30±13 vs. 38±13%); cardiac index was lower and mean pulmonary artery pressure significantly higher (p 0.0001).

Patients with IMR had a greater extent of severe (> 2SD) asynergy (58±21 vs 52±16%, p = 0.001) and a reduced systolic EI (0.769±0.01 vs 0.809±0.01 p = 0.002). Systolic curvature and fractional shortening are shown in Fig. 1. Shortening is lower and curvature is flattened at inferior regions (stars indicate significance)



Patients with IMR have greater systolic sphericity and worse hemodynamics. Inferior curvature and wall motion abnormalities are strictly related and characterize patients with MR. Systolic shape abnormalities are independent of volumes. Regional inferior flattening and reduced shortening could be considered as a further mechanism of IMR.

P3670 Long-term changes in systolic and diastolic function and serum markers of collagen synthesis in patients with post-infarction left ventricular remodelling

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Background: Left ventricular (LV) remodeling after AMI is thought as a progressive phenomenon leading to heart failure. The occurrence of such a transition and its time course vary greatly and most of the informations stem from studies on thrombolyzed patients (pts). However, long-term serial changes in systolic and diastolic function, as well as in serum markers of collagen synthesis, have been poorly investigated among pts successfully reperfused by primary PTCA. OBJECTIVE: To assess serial late changes in echo LV geometry and function, and in serum values of procollagen type I and III in asymptomatic pts with and without post-infarction LV remodelling. METHOD: 48 consecutive pts with AMI treated with primary PTCA, 14 pts (group 1) with and 34 (group 2) without early (6 months) LV remodeling (change in LV end-diastolic volume from baseline to 6 months > 20%), underwent the following examinations: 1) coronary angiography at 6 month, 2) echo-Doppler assessment of systolic function (LV end-diastolic volume - LVEDV, LV end-systolic volume- LVESV, LV ejection fraction- LVEF, LV eccentricity and mass index) and diastolic function (E and A wave peak; E/A ratio, isovolumetric relaxation time - IVR, deceleration time of early LV transmitral flow - DT), and 3) serum measurements of procollagen type I and III (as an indirect marker of collagen shyntesis) at 2,5 and 5 years of follow-up. RESULTS: Baseline anagraphic and clinical characteristics, and 6-month angiographic results were similar in two groups. Six month LV systolic geometry/function, but no diastolic function were significantly worse in group 1 that in group 2 (LVEDV: 101 ± 31 ml vs 63 ± 22 ml, p < 0.001; LVESV: 68± 28 ml vs 35 ± 20 ml, p < 0.005; LVEF: 36% ± 10 vs 49% ± 14, p < 0.005). From 6 month to 5 years, LV volumes, LVEF and eccentricity indexes shown a slight and non significant improvement in both groups. On the contrary, LV mass (101 g/m^2 ± 31 vs 81 g/m^2 ± 24, p < 0.03), Doppler indexes of reduced LV compliance (DT: 169 ± 56 msec vs 201 ± 32 msec, p < 0.03), and changes in serum procollagen type 1 (60 ± 64 vs -1,6 ± 59, p < 0.008) were significantly increased in group 1 compared with the group 2. CONCLUSION: Among pts reperfused with primary PTCA systolic function and geometry remain stable both in pts with and without early (6-month) LV remodeling. However pts with 6-month LV remodeling show peculiar adverse long-term changes in LV mass, diastolic function, and plasma markers of collagen synthesis. Large-scale studies are needed to assess if these changes will translate in a worse prognosis.

P3671 Beneficial effect of preinfarction angina on ventricular remodelling after mechanical reperfusion for acute myocardial infarction

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Background: The effects of preinfarction angina (PA) on infarct size, postinfarction left ventricular (LV) function and clinical outcome, particularly in pts with myocardial infarction (MI) treated with mechanical reperfusion, has not been fully clarified. Thus, we sought to determine the relationship between PA (within 7 days before MI) and myocardial damage, LV functional recovery and 6-month LV remodeling in a large series of patients (pts) with acute myocardial infarction (MI) treated with primary PTCA.
Methods: We serially evaluated 317 consecutive pts who underwent successful primary PTCA for acute MI (TIMI 3 flow in the infarct-related artery and residual stenosis <30%) by 2-dimensional echocardiography (within first 72 hours, and at 1 and 6 months following MI). LV volumes (determined by Simpson's biplane formula), ejection fraction (EF), and infarct zone wall motion score index (IZ-WMSI) were calculated for each study. Coronary angiography was repeated at 6 months in all pts.
Results: PA was detected in 112/317 (35%) pts. Baseline echocardiographic and clinical data as well as the therapy during follow-up period were similar in pts with and without PA. Peri- and postprocedural angiographic data (extent of coronary artery disease, collateral circulation, time to restored TIMI 3 flow, and late restenosis and reocclusion rates at 6 months) were also similar for the groups with and without PA. Peak creatine phosphokinase level was lower in pts with than without PA (2395±1818 vs. 3025±2269 IU, p=0.013). According to ANOVA, pts with PA did not change LV end-diastolic volumes (from 122±37 to 123±39 ml, p=NS) and slightly decreased end-systolic volumes during the follow-up period (from 70±29 to 64±36 ml, p=NS). In pts without PA, LV end-diastolic volumes increased from 1 month on (from 125±40 to 133±48 ml, p=0.009), and were significantly larger as compared to pts with PA at 6 months (133±48 vs. 124±39 ml, p=0.013). EF improved in both groups during follow-up (from 44±9 to 51±13%, p=0.0002, and from 43±10 to 50±12%, p=0.0002, in pts with and without PA, respectively) as well as IZ-WMSI (from 2.3±0.4 to 1.7±0.7, p=0.0001, and from 2.3±0.5 to 1.8±0.6, p=0.0002, in pts with and without PA, respectively).
Conclusions: PA may limit myocardial damage in pts treated with successful primary PTCA. It appears that PA may have inhibiting effect on LV remodeling during 6 months following acute MI.

P3672 Left ventricular remodelling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine

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Background: Coronary stent implantation during primary coronary angioplasty for acute myocardial infarction (AMI) has been shown to result in lower rates of recurrent ischemia and subsequent target vessel revascularization. Recent trials have described preserved left ventricular (LV) function and improved outcome with the combined use of abciximab and stent implantation, via protection from distal microembolization. Similarly, intracoronary adenosine bolus administration during primary angioplasty has been reported to reduce the incidence of no reflow. Objective: To evaluate the efficacy of standard abciximab treatment vs. intracoronary adenosine administration in preventing LV remodelling after AMI.
Methods: 65 patients (57 men and 8 women; mean age 57±11 years) presenting with a first AMI (<6 hours from symptom onset) and treated with primary PTCA with coronary stenting were randomized to abciximab treatment (0.25 mcg/kg bolus plus 12 hours infusion; ABCX, n=25), intracoronary adenosine (4 mg after balloon inflation; ADO, n=24), or conventional therapy (CONTROL, n=25). Patients with cardiogenic shock were excluded. The study end points included angiographic results (final corrected Thrombolysis In Myocardial Infarction [TIMI] frame count and a composite end point of slow and no-reflow or distal embolization), and 6-month echocardiographic results (% change in LV ejection fraction [LVEF], end diastolic volume [LVEDV], end systolic volume [LVESV], and wall motion score index [WMSI] compared with hospital admission).
Results: Baseline clinical, angiographic, and echocardiographic characteristics were similar in the 3 groups. A final TIMI grade 3 flow was achieved in 95% of patients, without significant differences in mean final corrected TIMI frame count among the 3 Groups (21±6 vs. 28±20% ADO vs. 25±10% CONTROL; p>0.2). A slow flow or no-reflow was observed in 2 ADO patients. At 6-month follow-up, ABCX patients showed a lower increase in LVEDV (1±10% vs. 10±16% ADO vs. 3±18% CONTROL; p=0.01) and a higher increase in WMSI (19±18% vs. 10±14% ADO vs. 9±16% CONTROL; p=0.04).
Conclusion: In patients undergoing primary angioplasty with coronary stenting for AMI, the use of abciximab, but not of intracoronary adenosine, results in a significant reduction of LV remodelling at 6 months, probably via protection from microvascular injury.

P3673 Beyond TIMI-3 flow and myocardial blush: myocardial perfusion assessed by MPI immediately after primary percutaneous coronary intervention predicts final infarct size

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Background: Impaired tissue perfusion, despite normalized epicardial flow (TIMI 3), is a predictor of adverse outcome in patients with acute myocardial infarction. Techniques enabling identification of such patients are required to evaluate possible treatment regimes to enhance perfusion. Corrected TIMI frame count (CTFC) and myocardial blush grade (MBG) have been suggested as indicators of successful reperfusion. We investigated the association between CTFC, MBG and an acute perfusion scan (MPI), and these parameters' ability to predict the final infarct size.
Methods: Sixty-one patients (59±6 years) treated with primary PCI (pPCI) achieving TIMI 3 flow in the infarct related artery (IRA) were included. MPI (99mSestamibi SPECT) defect size, CTFC and MBG were estimated immediately after successful pPCI. MPI was analyzed blinded to clinical and angiographic data, and perfusion defects were quantified and reported in percents of the left ventricle. The final angiography was analyzed at an independent angiographic core laboratory. MBG was scored as grade 3=normal, 2=reduced, and 0/1=absent or minimal. Final infarct size was assessed by MPI 3 months after treatment. Peak LDH was used as an alternative and independent assessment of infarct size. Correlations were tested by Spearman's Rho (Rho).
Results: IRA was LAD, CX and RCA in 41, 5 and 54% respectively. Median time from pain to reperfusion was 235 [95-751] minutes. MBG was 3, 2, 0/1 in 37, 16, and 8 patients respectively. Mean CTFC was 25±13 frames. The mean acute perfusion defect was 29%±15% [0-61%]. The acute perfusion defect correlated to MBG (Rho=0.37, p=0.003), but not to CTFC (Rho=0.12, p=0.40). Mean final infarct size was 14%±11% [0-45%] and mean peak LDH was 1782±1046 U/l. There was a good correlation between these measures (Rho=0.8, p<0.001). CTFC and MBG were not correlated to final infarct size either by MPI or peak LDH (Rho=0.11-0.24, p=0.09-0.50). The acute perfusion defect was a very strong predictor of final infarct size using either methods (LDH: Rho=0.77, p<0.001, MPI: Rho=0.88, p<0.001).
Conclusion: In the clinical setting acute MPI can serve as a useful tool for early identification of patients, who despite epicardial TIMI 3 flow have inadequate tissue level perfusion. MPI performed immediately after pPCI accurately predicts final infarct size and thereby enables possible interventions to enhance tissue level perfusion.

P3674 Coincidental fluctuation of circulating amyloid beta 42 and tissue inhibitor of metalloproteinases 1 after a severe acute myocardial infarction

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Background: Amorphous, non-filamentous deposition of circulating vasoconstrictive amyloid beta ending at 42 amino acid (Abeta42) has been recently described in peripheral blood vessels and non-neural tissues and could cause oxidative stress-mediated local cellular toxicity. Elevation of circulating Abeta42 and altered vascular and smooth muscle cell basement membrane protein metabolism (BMPM) are both considered as requriments for peripheral Abeta42 deposition. Aim of the present study was to delineate whether a severe acute myocardial infarction (AMI) possibly provide conditions associated with altered BMPM that might provoke deposition of circulating Abeta42.
Methods: In 21 patients (pts) with first attack of AMI, large infarct size, ejection fraction <45%, no evidence of any later thrombotic occlussion or extension of myocardial necrosis, serum levels of Abeta42 and tissue inhibitor of metalloproteinases 1 (TIMP-1), previously described as an estimate of AMI-induced extracellular matrix remodeling, were determined on hospital admission [mean latency from the onset of chest pain: 2±1 hours (h)] before thrombolysis (0h) and after 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 72h, 4 days (d), 5d, 7d, 15d and 30d and compared to corresponding values of 20 age- and sex-matched healthy controls (HS).
Results: At 0h, Abeta42 levels were higher in comparison to those of HS (26.7±1.1 vs 1.3±0.3 pg/mL, p=0.001). After that, a gradual drop of Abeta42 levels to their lowest values at 6h (18.2±7.8 pg/mL) was followed by a progressive elevation of them to their highest values at 30d (35.9±6.4 pg/mL), (in both cases $p<0.05$ in comparison to the respective levels at 0h). In addition, TIMP-1 levels at 0h were lower than those of HS (582±74 vs 710±24 ng/mL, $p<0.04$). After that, they increased sharply at 6h (763±46 ng/mL), peaked at 36h (780±40 ng/mL) (in both cases $p<0.001$ in comparison to the respective levels at 0h) and then declined to normal values, reaching them on 5d (672±37 ng/mL). Negative correlations between Abeta42 and TIMP-1 levels were detected at 24h (r=-0,71, p=0,03 and at 48h (r=-0,82, p=0,0001) after the onset of chest pain.
Conclusions: Severe AMI induces coincidentally elevation in circulating Abeta42 and alterations in BMPM during the first 5 days from the onset of chest pain. This may enhance the potential of Abeta42 peripheral deposition, especially at 24h and 48h after the onset of chest pain, that could cause oxidative stress-mediated local damage and reduce local blood flow, further increasing oxidative stress and upregulating Abeta42 peripheral production.

P3675 Left ventricular function, myocyte injury markers, inflammatory status and MRI-determined no-reflow in post-myocardial infarction patients

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Aim: The extent of microvascular obstruction during acute coronary occlusion referred to as the no-reflow phenomenon could determine the magnitude of myocardial damage and thus patient (pts)prognosis after myocardial infarction (MI). Areas of no-reflow at the infarct core were assessed in order to determinate the factors that could predict the amount of no-reflow. Methods: Using contrast-enhanced MRI (5-7 slices, 10mm thick encompassing the whole left ventricle), no-reflow was defined as early hypoenhancement (2 to 3 minutes after iv gadolinium) in post-MI patients. The contrast defect was scored from 0 (no hypoenhancement) to 3 (strong hypoenhancement). Results: 50 patients (mean age 56±11 yrs; 78% men) with documented acute MI underwent coronary angiography and contrast-enhanced MRI (6±2 days after MI) and were evaluated with biochemical parameters. No-reflow (score 1 to 3) was observed in 88% of the pts. Major no-reflow phenomenon (score 2-3) was found in 54% of the group. No-reflow intensity was positively related to peak CPK (rho=0.44; $p<0.003$), peak Troponin I (rho = 0.43; $p<0.003$) and negatively to LVEF (rho = -0.44; $p<0.02$). Low TIMI grade (<3) was well predictive of the extent of no-reflow: 79% of these pts had a no-reflow score > 1. However TIMI 3 grade was a weak predictor of the absence of no-reflow. The TIMI grade was also barely related to LVEF (rho = 0.30; $p<0.04$). Cardiovascular risk factors were not predictive of no-reflow occurrence. Baseline inflammation status assessed by plasma C-reactive protein and leukocytes were significantly related to the extent of no-reflow (rho = 0.43 and rho = 0.44; $p<0.003$), and inversely to the LVEF (rho = - 0.30; $p<0.04$). Leukocytes and peak Troponin I were also significantly correlated (rho = 0.44; $p<0.002$). Conclusion: MRI-detected no-reflow, is confirmed as a determinant of post-MI LVEF and moreover appears related to the inflammatory status at the admission. This later aspect already pointed out in experimental studies deserves further investigations in the clinical setting.

P3676 The effect of percutaneous myocardial revascularization on myocardial perfusion, glucose metabolism and ischaemia

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Background: Percutaneous myocardial revascularization (PMR) has emerged as an alternative treatment for patients with severe angina non-amenable for coronary revascularization. We studied the effect of PMR on myocardial perfusion and glucose utilization.
Methods: 18 consecutive patients (mean age 59 ± 10 years, 17 males) underwent PMR. Prior and six months postPMR left ventricular ejection fraction (LVEF) using radionuclide ventriculography, dobutamine stress echocardiography (DSE) and single-photon emission computed tomography (SPECT) with 99m-technetium-tetrofosmin (perfusion) and 18-F-fluorodeoxyglucose (glucose utilization) were performed. Both DSE and SPECT tests were scored semiquantitatively using a 16-segment model and respectively a 5- and 4-point score.
Results: PriorPMR 132/288 (46%) segments showed an ischemic response during DSE of which 90 (68%) were eligible for treatment. Canadian Cardiovascular Society Score for angina decreased from 3.4 to 2.4 ($p<0.01$) at six months. PostPMR LEVF was unchanged, 47 ± 7% vs. 49 ± 7% ($p = 0.1$). PMR-treated segments compared to non treated ischemic segments showed: (1) an increased wall motion score at rest, 2.11 to 3.00 ($p<0.01$) vs. 2.05 to 2.10 ($p = 0.1$); (2) a reduced myocardial perfusion, 14 (14%) treated segments compared to 1 (3%) non-treated segments ($p = 0.02$); and (3) a reduced glucose utilization, 18 (20%) treated segments compared to 1 (3%) of non-treated segments ($p<0.01$).
Conclusions: Conversion of ischemic myocardium to infarcted myocardium was observed after PMR in a significant number of treated ischemic segments, which may explain the reduction of angina.

P3677 Assessment of residual myocardial viability in regions with chronic electrocardiographic Q-wave infarction

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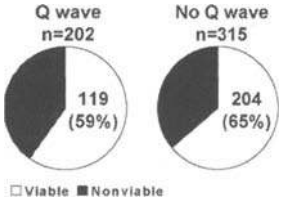
Background: Q waves on the ECG are often considered to be reflective of irreversibly scarred myocardium, as a result of antecedent transmural myocardial infarction. However, there are some indications that residual viable tissue may be present in Q wave infarcted regions. It is important to know how many Q wave regions contain viable tissue, since patients may benefit from revascularization in terms of improvement of function and long-term survival.
Methods: Patients (n=150) with chronic electrocardiographic Q wave infarction, heart failure symptoms and chronic coronary artery disease underwent dobutamine-atropine stress echocardiography (DSE) to assess myocardial viability. Residual viability in regions with Q wave infarction was considered present when the end-diastolic wall thickness (EDWT) was >6 mm and the response during dobutamine infusion indicated viable tissue.
Results: Baseline echocardiography revealed 517 dysfunctional myocardial regions, 202 of the dysfunctional regions were related to Q waves on the ECG, the other 315 dysfunctional regions were not. EDWT was <6 mm in 13 regions with a Q wave on the ECG, with only 1 region exhibiting viable tissue during DSE. EWT was >6 mm in 189 regions with a Q wave with 118 (62%) having viable tissue on dobutamine stress echocardiography. In 6 dysfunctional regions without a Q wave EDWT was =6 mm with all being nonviable on DSE; of the 309 regions without a Q wave and EDWT >6 mm, 204 (66%) exhibited viability on DSE.



Viability in infarcted regions.

Conclusion: 59% of dysfunctional regions related to chronic Q waves exhibit viability on dobutamine stress echocardiography. EDWT <6 mm virtually excludes viability; regions with EDWT >6 mm need additional testing to detect/exclude viability.

P3678 Response to dobutamine in function, myocardial perfusion, and fatty acid metabolism for predicting the reversible infarct-related myocardium

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Background: Although low-dose dobutamine stress echocardiography (LDDS), assessment of myocardial perfusion, and activity of fatty acid metabolism using nuclear procedure predict the reversible dysfunction myocardium after myocardial infarction (MI) respectively, the relative merit among these 3 parameters has not been evaluated at a time in acute phase. The aim of this study was to investigate the significance of each parameter and these relative merit.
Methods: We studied 45 patients (60.7 ± 10.4 yrs.) who underwent successful revascularization within 24 hour after the onset of MI (5.4 hours from 1 to 24 hours) and who were confirmed no restenosis by coronary arteriography after 1 year. Thallium-201/I-123 beta-methyl-branched fatty acid (BMIPP) dual-isotope SPECT was performed with LDDS (5 to 10 mg/kg/min) within 1 week after MI (4.8 ± 1.7 days). Final functional improvement was evaluated on echocardiography at 1 year. Segmental wall motion was scored on 3 grades as normal, hypokinesis, akinesis or dyskinesis. An abnormality with SPECT images in each tracer was quantitatively scored as ranged from 0 to 4. Viability was defined in each, LDDS; a score change more than 1 grade, thallium-201; the change to % uptake during dobutamine stress from that by redistribution images or score 0 (normal), thallium-201/BMIPP; a mismatch of 2 tracers during dobutamine stress or score 0 of either tracer.
Results: In 93 dyssynergic infarct-related segments within 1 week after revascularization, viability was detected in 46 segments by LDDS (49.5%), in 44 segments by thallium-201 (47.3%), and 44 segments by thallium-201/BMIPP (47.3%). The sensitivity, specificity and accuracy for predicting the functional improvement by LDDS (81.3%, 68.3%, and 72%) were higher than that by thallium-201 (62.5%, 60.7% and 61.3%) or by a mismatch of thallium-201/BMIPP (62.5%, 60.7% and 61.3%). The sensitivity and accuracy by LDDS were increased in the segments in which viability was detected by only thallium-201 (44 segments) or by thallium-201/BMIPP (44 segments) (85%, 66.7% and 75%, or 90%, 62.5% and 75% in order). In 35 segments in which viability was detected by 2 methods using SPECT imaging, these by LDDS were increased remarkably (93.9%, 63.2% and 77.1% in order).
Conclusions: The positive response to adrenergic stimulation with low-dose dobutamine in wall motion predict the functional recovery of MI more accurately than that in 2 methods with SPECT imaging, but the more accurate prediction was filled by the recovery of oxidative metabolism and cell menbrane integrity in stunning myocardium.

P3679 High myocardial strain rate during isovolumic relaxation phase identifies viable myocardium after reperfusion in acute myocardial ischaemia

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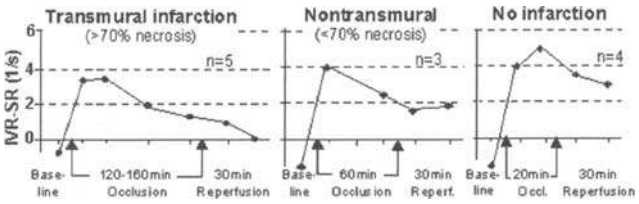
Postsystolic thickening (PST) is a marker of ischemia and, potentially, of viability. PST can be detected by abnormally high intramyocardial strain rates (SR) during the isovolumic relaxation phase (IVR). We tested whether IVR-SR correlates with the content of viable myocardium after acute myocardial ischemia.
Methods: Twelve open-chest pigs were subjected to LAD occlusion (20-160 min) followed by reperfusion (30 min). Tissue Doppler velocities (>150 frames/sec) of the anterior LV wall were collected from within the LV cavity using an 8.5 MHz intracardiac ultrasound catheter. Radial strain rates and systolic strain were obtained from ischemic and normal adjacent myocardium. Transmural extent of necrosis (TEN) was quantified from TTC-stained cardiac specimens. Alignment of ultrasound and cardiac specimen data was assured by placing, at baseline, 2 epicardial echogenic markers on the interrogated wall.
Results: Systolic strain was severely reduced during ischemia and reperfusion as compared with baseline (-5±3%, 3±2%, and 38±6%, respectively). IVR-SR consistently increased during ischemia, and persisted high in walls with viable myocardium (Figure). In animals with a transmural infarct, IVR-SR progressively decreased during the occlusion period and at reperfusion (figure). End-diastolic wall thickness, as measured using gray-scale M-mode, increased 30 min following reperfusion in proportion to TEN (r=0.75, p<0.0001). IVR-SR at reperfusion was inversely related to both TEN (r=-0.82, p<0.0001) and change in end-diastolic wall thickness (r=-0.79, p<0.0001).



Conclusions: In reperfused myocardial infarcts with severely reduced systolic strain, presence of PST identifies viable elastic myocardium while its absence reflects a stiff transmurally infarcted myocardial wall.

P3680 The PURSUIT risk score correlates with ejection fraction and angiographic findings in non-ST elevation acute myocardial infarction

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Background: In patients with non-ST elevation acute myocardial infarction (NSTEMI), a higher PURSUIT risk score is associated with higher mortality. We tried to determine if the PURSUIT risk score also correlates with predischarge ejection fraction (EF) and with angiographic severity of coronary artery disease (CAD).
Methods: The PURSUIT risk score was calculated for 337 consecutive Olmsted County, Minnesota, patients with NSTEMI admitted to the coronary care unit of our institution between 1988 and 1998. After excluding patients with prior coronary bypass surgery (n=42), 219 patients (65%) had coronary angiography within 30-days from admission. A predischarge EF measurement was available on 246 patients (73%).
Results: Mean age was 70 ± 13 years, and 37% of the patients were women. Mean predischarge EF was 52 ± 16%. Patients with higher PURSUIT risk score had lower EF (p<0.001, Kruskal-Wallis test, Table). Three-vessel (>=70% stenosis in all 3 coronary arteries), or left main (>=50% stenosis) CAD was present in 66 of 219 (30%) patients who underwent coronary angiography. The mean ± SD CAGE 50 score (number of CASS (Coronary Artery Surgery Study) segments with >=50% stenosis) was 4.3 ± 2.6. A higher PURSUIT risk score was associated with greater likelihood of 3-vessel or left main CAD (p<0.001, chi-square test), a higher CAGE 50 score (p<0.001, Kruskal-Wallis test), and higher 30-day mortality (p<0.001, chi-square test) (table).
Conclusions: The PURSUIT risk score correlates not only with mortality but also with predischarge ejection fraction and with angiographic severity of CAD in nonselected, community-based patients with NSTEMI. Early coronary angiography should be considered for NSTEMI patients with a high PURSUIT risk score that are candidates for revascularization, since they are very likely to have 3-vessel or left main CAD.

Abstract P3680 – Table

	PURSUIT risk score						P
	0-4	5-8	9-12	13-16	17-20	>20	
EF (%), mean (SD)	59 (12)	57 (13)	54 (15)	45 (12)	38 (16)	33 (5)	<0.001
3-vessel or left main disease, n (%)	3/34 (9%)	10/66 (15%)	17/63 (27%)	23/37 (62%)	9/15 (60%)	4/4 (100%)	<0.001
CAGE 50 score, mean (SD)	2.9 (1.9)	3.7 (2.3)	4.4 (2.4)	5.4 (2.7)	5.8 (2.4)	7.3 (2.2)	<0.001
30-day mortality, n (%)	0/39 (0%)	1/85 (1%)	9/108 (8%)	9/60 (15%)	5/31 (16%)	6/14 (43%)	<0.001

P3681 Myocardial perfusion in real-time using power modulation. An in-vivo evidence for a microcirculatory damage after acute myocardial infarction

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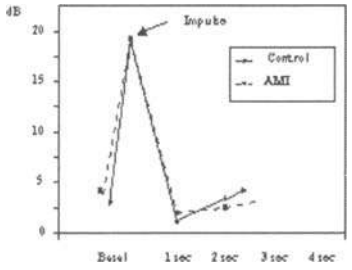
Recently, myocardial contrast echocardiography (MCE) have shown to be capable to evaluate the myocardial microvasculature status by measuring flow reserve during the administration of vasodilator stimuli. The objective of this study was to evaluate the usefulness of MCE in detecting the microvasculature abnormalities that occur after acute myocardial infarction (AMI) by using real-time MCE at baseline without the necessity of vasodilator stimuli.
We studied 89 myocardial segments in 16 patients (11 with recent AMI and 5 control subjetcts with normal coronary arteries angiographically demonstrated). The Power-Modulation technique (Agilent 5500 equipment) was used. This technique combines low (0.1) and high (1.7 for 5 frames) mechanical index. A quantification system (Quanticom, Echotech, Germany) was used. The velocity of contrast refilling was calculated with the following formula: (Ip - I1 sec)/tp - 1, where Ip is the peak refilling videointensity, I1 sec the intensity 1 sec after the high-mechanical index impulse to the time of peak videointensity
Myocardial segments in AMI patients showed a significantly reduced contrast refilling velocity in comparison with control subjects (1.41±2.16 vs 2.69±2.48, $p<0.05$) (see figure).



MCE in AMI vs control subjects.

Conclusion: This low-index, real-time MCE tecnique allows an in vivo demonstration of the abnormalities that occur in the myocardial microvasculature of patients with AMI, with the administration of i.v. contrast agents and without the necessity of vasodilator stimuli.

P3682 Left ventricular segmental motion and perfusion myocardial contrast echocardiography analysis in the acute phase of coronary ischaemic syndromes

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Doppler echocardiography with the administration of new myocardial contrast enhancement agents (MCE) has been applied in a large number of cardiac pathologies including the evaluation of left ventricular (VE) myocardial perfusion post acute coronary syndromes (ACS). MCE clinical impact has not yet been established in ACS. Our aim was to assess the clinical utility of the initial MCE study (day 1) in ACS patients (pts). We evaluated 54 pts with ACS clinical and laboratorial diagnosis, mean age 62±13 yrs (44-72 yrs), 56% male, submitted to B-mode echocardiogrphy, second harmonic (2H) and MCE imaging, destruction technique, PCI software, Doppler "power angio", MCE agent Levovist® 4g/300mg/ml. 2H MCE studies were performed <24 hours post CCU admission. 2H MCE studies were analysed in 3 apical LV views, transferred to a cine-loop digital memory, 0.8 mechanical index, delta 2 function, endocardial contour 3 level, 1:4 cycles synchronization and optimisation of the B-mode imaging. 864 LV myocardial wall segments were analysed according to the ASE classical model. We assessed the LV regional wall motion abnormalities (normal-0, hypo-1, aqui-2 e disquinesia-3, aneurysm-4) and calculated the wall motion index (WMI) by 2H MCE. In the same We established the LV segmental MCE perfusion pattern (normal-2, heterogeneous-1 and absent-0) and calculated the MCE perfusion index (MCEI). Pts were submitted to coronary angiography to assess the extension and degree of coronary artery disease severity (single- vs. multivessel). Type 2 MCE pattern was found in 59,1%, type 1 in 23,3% and type 0 in 17,5% of the LV myocardial wall segments. LV MCEI registered an inverse correlation with the WMI (r=-0.44; $p<0.01$). Single vessel disease was detected in 23,1% and multivessel in 76,9% of pts.
MCE is a noninvasive technique with the potential to identiphy the extension and degree of severity of the LV myocardial microcirculation involvement in the acute phase of ACS.

MCE Results

MCE	Normal	Hypoquinesia	Aquinesia	Dysquinesia	Singlevessel	Multivessel
Pattern 2	94.9%	16.3%	10.2%	0.0%	85.4%	51.5% *
Pattern 1	5.1%	51.1%	43.8%**	35.4%*	9.9%	27.3%*
Pattern 0	0.0%	32.5%*	45.8%	64.5%	4.6%	21.4%
p value	p=0.01	*p<0.01	p=0.03	**p=0.04		

P3683 Right ventricular function in patients with left ventricular infarction

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Introduction: Patients with acute myocardial infarction (AMI) may develop right-side signs and symptoms. We evaluated right ventricular (RV) function in patients (pts) with a left ventricular (LV) AMI and no RV involvement.
Methods: We studied RV function using Doppler Echocardiography in 22 pts (mean age 56±4) with LV-AMI and no ECG signs of RV involvement. Seven pts had anterior AMI, five pts lateral AMI and ten pts inferior AMI. Echo-Doppler examination was performed on admission and two months after the acute event. All pts were thrombolysed, had an uncomplicated course and stayed only on medical treatment until the second study. We evaluated RV (diastolic) function from the transtricuspid and transpulmonary velocity curves and measured the E wave, the A wave, decceleration time of the E wave, isovolumic relaxation time, E/A ratio and the myocardial performance index (TEI index) of the RV. Twenty two age and sex matched normal individuals comprised our control group. Statistical analysis was performed using t-test and statistical significance was defined as a p value <0.05.
Results: There were no statistical differences concerning the location of the AMI. The table reviews all relevant data.

RV indices	Controls (n=22)	Patients on admission (n=22)	p	Controls (n=22)	Patients at 2 months (n=22)	p
E wave (m/sec)	0.581±0.13	0.380±0.25	<0.001	0.581±0.13	0.498±0.18	NS
A wave (m/sec)	0.440±0.04	0.320±0.27	<0.001	0.440±0.04	0.364±0.22	NS
E/A	1.35±0.11	1.16±0.24	NS	1.35±0.11	1.35±0.19	NS
DT (sec)	0.124±0.011	0.237±0.12	<0.001	0.124±0.011	0.168±0.14	NS
IVRT (sec)	0.031±0.025	0.048±0.07	<0.001	0.031±0.025	0.034±0.038	NS
MPI	0.264±0.14	0.364±0.18	<0.001	0.264±0.14	0.278±0.18	NS

RV indices in pts with a LV-AMI versus controls on admission and two months after the acute event.

Conclusions: Patients with LV-AMI and no RV involvement on the surface ECG, exhibit impairment of RV systolic and diastolic function as assessed by the MPI and RV indices. There is spontaneous improvement of these indices after two months towards normal values.

P3684 New method for quantification of the baroreflex in post infarction patients

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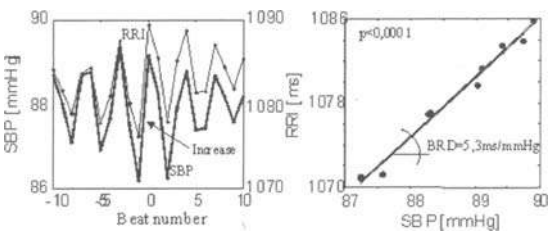
Objective: To demonstrate a new method for quantification of the baroreflex.
Methods: In 69 post-MI patients, simultaneous 30 minutes recordings of ECG and arterial blood pressure (Portapres®) were derived. The new method selects systolic arterial blood pressure (SBP) waves which are higher than the preceding SPB wave and calculates the mean fluctuations of RR intervals (RRI) and of SBP before and after the SBP increase. The slope of the regression line of the first ten values of RRI and SBP after the increase of SBP is used as measure of baroreflex dynamicity (BRD).
Results: The fluctuations in RRI are closely coupled to the fluctuations in SBP (Figure 1). Accordingly, there was a close correlation of RRI and SBP (Figure 2). BRD was highly correlated with Heart Rate Turbulence Slope (r=0,69, $p<0,0001$, not shown).



Conclusion: The new method allows a non-invasive quantification of the baroreflex function.

P3685 Functional recovery of akinetic segments post acute myocardial infarction. The role of myocardial contrast echocardiography

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Myocardial contrast echocardiography (MCE) is a new imaging technique that can perform a non invasive analysis of the coronary microcirculation during acute myocardial ischemia and infarction (AMI). Purpose: To assess the MCE distribution post AMI on the potential recovery of LV myocardial wall segments with abnormal wall motion (AWMS). Methods: We evaluated a sample population of 54 pts submitted to MCE study <24 h post AMI, using a Sequoia C256 (Acuson, CL, USA) ultrasound equipment, intermitent imaging, 1:4 cycles acquisition, destructive method, PCI software, Doppler angio mode, delta function 2, edge function 2, 3V2c 4 MHz probe, 0.8 mechanical index, after Levovist® 4g-300 mg/ml (Schering AG, Germany) intravenous injection. A pair of MCE images, corresponding to the destruction and perfusion phases were compared. Hypokinetic and akinetic LV myocardial wall segments with >6 mm thickness were identified and the MCE pattern evaluated (normal-2; patchy-1; absent-0). AWMS of the LV myocardium included both hypokinetic and akinetic LV myocardial wall segments. LV wall segments with <6 mm thickness were not included in this MCE study. Several LV parameters were analysed, such as the number of AWMS per pt, the total number of LV myocardial wall segments with MCE pattern 0 (P0), 1 (P1) and 2 (P2) per pt, the number of MCE pattern 0, 1 and 2 per pt among AWMS, the LV end-diastolic (LVDV-ml) and endsystolic (LVSV-ml) volumes and its derived LV percent ejection fraction (LV%EF-%). The recovery of LV segmental function and LV%EF were analysed at >6 months follow-up. The LV%EF variation (LV%EF Var-%) was also calculated as this variable difference between <24 hours and 6 month studies. Results: 92% (48/52)pts were evaluated at >6 months follow-up. Significant direct correlations were obtained between LV%EF and the total number of P2/pt (r=0.55; p=0.01) and P2 AWMS/pt (r=0.63; p<0.01). Significant inverse correlations were obtained between LV%EF and the total number of P0 and P1/pt (r=-0.44 and -0.47; p=0.04-0.03) and P0 and P1 AWMS/pt (r=-0.51 and -0.56; p=0.01 and <0.01). The LV%EF at >6 months period and LV%EF Var were related mainly with the number of P1/pt (r=0.66 and 0.70; p<0.01) and P1 AWMS/pt (r=0.68 and 0.72; p<0.01). Conclusions: The recovery of left ventricular segmental wall motion and global function post AMI was related with the presence of a particular pattern of myocardial contrast echocardiography. The functional recovery of the LV myocardium post AMI can be already assessed by myocardial contrast echocardiography at an early phase of the acute coronary event.

ANTITHROMBOTIC/THROMBOLYTIC AGENTS

P3686 Recombinant P-selectin glycoprotein ligand-Ig enhances the thrombolytic effect of alteplase, reteplase, and streptokinase in a canine model

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Platelet-leukocyte interactions, mediated by P-selectin on platelets and its high affinity ligand P-selectin Glycoprotein Ligand-1 (PSGL-1) on leukocytes, lead to tissue factor release and fibrin generation and hence are important in thrombus stabilization and amplification. We have previously demonstrated that P-selectin antagonism using rPSGL-Ig, a recombinant soluble form of PSGL-1, in conjunction with alteplase, significantly accelerated thrombolysis and prevented reocclusion in a porcine model. In this study, the efficacy of rPSGL-Ig in enhancing the thrombolytic effect of alteplase (tPA), reteplase (rPA) and streptokinase (SK) was studied in a canine model of thrombolysis. Occlusive thrombus formation was induced by placing a copper coil in the left internal iliac artery of 12-15 kg mongrel dogs under fluoroscopic guidance. All animals received aspirin (2 mg/kg IV) prior to coil placement and heparin (70 U/kg bolus+15 U/kg/hr infusion) immediately upon coil occlusion. After 15 min, thrombolytic therapy was initiated using tPA (1.5 mg/kg IV, 8% as an initial bolus, remaining infused over 90 min), rPA (2 IV bolus injections of 0.17 U/kg 30 min apart) or SK (23,000 U/kg IV infused over 60 min). Ten minutes after initiation of the thrombolytic, animals received a single IV bolus of either vehicle (n=6, 10, 7 for tPA, rPA and SK respectively) or rPSGL-Ig at 500 μg/kg (n=6, 7, 7 for tPA, rPA and SK respectively). Blood flow through the artery was monitored by angiography every 10 min for 3 hr and was graded on a scale 0-3. In control animals, thrombolysis was achieved in 55±7.6 (mean±SEM), 60±10.4, and 50±4.9 min with tPA, rPA and SK respectively. rPSGL-Ig reduced time to lysis with the three lytics by 55% (p=0.002), 55% (p=0.02), and 46% (p=0.004) respectively. rPSGL-Ig also increased the post-lysis percent time with near normal (score 2 or 3) blood flow from 38.1±8.5%, 38.5±10.2% and 35.1±11% to 74.3±14.1% (p=0.03), 88.4±11.6 (p=0.006) and 64.1±15.9% (p=0.16) in the tPA, rPA and SK groups respectively. Further, no increases in bleeding times (measured on the inner lip) and bleeding from incision sites was noted in rPSGL-Ig-treated vs control animals. These data demonstrate that P-selectin blockade with rPSGL-Ig modulates platelet-, leukocyte-mediated thromboinflammatory events, and enhances the thrombolytic effect of the thrombolytic agents tPA, rPA, and SK without increasing bleeding complications.

P3687 Superior clinical efficacy of clopidogrel compared to ticlopidine after successful coronary stenting: a meta-analysis of published studies

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Background: Combination therapy with aspirin plus ticlopidine has become the reference antithrombotic therapy after coronary stenting. However despite its effectiveness, ticlopidine has a significant incidence of severe side effects. Thus, clopidogrel, a ticlopidine analogous with an excellent safety profile, has been introduced in clinical practice. To date only few underpowered studies comparing the clinical efficacy of clopidogrel and aspirin versus standard combination therapy after coronary stenting have been performed and odds ratios (OR) vary substantially between them. Thus, the present investigation refines these values by means of a formal meta-analysis.
Methods: Ten studies were considered suitable for analysis. OR were calculated for 30-days follow-up in patients who had undergone successful coronary stenting. Primary end points were a composite of death and non-fatal myocardial infarction (MI) as well as a composite of major adverse side effects as considered in every single study. Secondary end points were a composite of major adverse cardiac events (MACE), according to single study definition, and individual cardiac events as well.
Results: A total of 11688 patients were included. At 30 days, the OR for death and non-fatal MI was 0,63 (95% CI, 0.47-0.85; p=0.003) in favor of patients treated with clopidogrel and aspirin. There was also a trend toward less MACE (p=0.1), less mortality (p=0.2) and less non-fatal MI (p=0.12) for patients treated with clopidogrel. Furthermore, OR for major adverse side effects was 0,53 (95% CI, 0.42-0.66, p<0.00001) in favor of patients treated with clopidogrel and aspirin. However, when the analysis was limited to the randomized trials, clopidogrel plus aspirin demonstrated less impressive advantage over standard therapy except for a better safety profile (OR 0.46, 95% CI 0.32-0.66; p=0.00002).
Conclusions: According to 30-day death and nonfatal MI rates, the present meta-analysis demonstrates that clopidogrel has a superior clinical efficacy compared to ticlopidine in patients who had undergone successful coronary stenting. In addition a significantly better safety profile than ticlopidine was reported, confirming on a larger scale the findings of the randomized comparative trials.

P3688 Enoxaparin in unstable angina patients who would have been excluded from randomized pivotal trials

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Background: Following ESSENCE and TIMI 11B trials, a large population with UA/NSTEMI is being treated with enoxaparin. However, many of these patients receiving enoxaparin would not have been eligible for these trials. The present study tried to identify and to describe this group of patients and examined the therapeutic options and the 1 month outcomes.
Methods and Results: In our center, all patients with UA/NSTEMI are anticoagulated with subcutaneous enoxaparin and followed-up for 1 month. Among 515 consecutive patients, we identified 174 patients ("EP" group for excluded patients)who would have not been eligible for ESSENCE or TIMI 11B according to 7 major exclusion criteria, including heart failure (n=82), chronic renal failure (creatinine clearance <30 mL/min, n=62), left bundle branch block (n=35), a recent history of stroke (n=20), recent surgery (n=19), cancer (n=20) and acute anemia (n=5). This "EP" group was older, had a higher female/male ratio, had more frequently a past-history of MI or a diagnosis of non-Q MI on admission in comparison patients without any of the exclusion criteria ("NEP" group). Coronary revascularization and the use of GP IIb/IIIa inhibitors were less frequent in the "EP" group than in the "NEP" group (24.7% vs 34.9%, $p<0.01$, and 4.6% vs 11.1%, $p<0.01$, respectively). The distribution of the anti-Xa activity was similar in both groups. Although the "EP" group were at higher risk of bleedings than the "NEP" group, the rates of bleedings (major and minor) at 30 days were similar in both groups (2.3%vs 2.9%, respectively, p=NS). After multivariate analysis, the use of GP IIb/IIIa inhibitors and hypertension were the only independent predictors of bleeding found in the whole population. Compared with the "NEP" group, the group of "EP" had also a higher risk profile for further ischemic events. Indeed, this group had a 4-fold increase rate of death or MI at 30 days (15.5% vs 4.1% for "EP" vs "NEP", respectively, $p<0.01$). After multivariate analysis, the independent predictors of death or MI at 30 days were NSTEMI on admission, creatinine clearance and heart failure.
Conclusion: Patients who do not fit the enrolment criteria of ESSENCE/TIMI 11B are at higher risk of both bleedings and ischemic events. In these patients, enoxaparin with dose-adjustment to creatinine clearance provides adequate anti-Xa levels and no excess of bleeding. However, these patients remain at high risk of recurrent ischemic events. Renal and heart failures were two strong predictors of poor outcome besides a positive troponin test on admission.

P3689 Inhibition of ADP-induced platelet-leukocyte conjugate formation by clopidogrel and AR-C69931MX

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Background: Platelet-leukocyte interactions are recognised to have pro-inflammatory effects, which may be important in the pathophysiology of ischaemic heart disease. Clopidogrel and the novel intravenous antithrombotic agent AR-C69931MX act at the level of the platelet P2Y12 receptor, which is known to amplify platelet activation, aggregation and other responses including expression of P-selectin, which is the dominant mediator of platelet-leukocyte conjugate formation via interaction with PSGL-1 on leukocytes.
Methods: ADP-induced platelet-monocyte and platelet-neutrophil conjugate formation, as well as P-selectin expression, were studied using hirudin-anticoagulated whole blood and flow cytometry with fluorescent-labelled antibody techniques (anti-CD14-RPE and anti-CD42a-FITC to identify platelet-leukocyte conjugates). Platelet aggregation was measured using whole blood single-platelet counting. We studied the effects of 10 days administration of clopidogrel 75 mg od, aspirin 75 mg od or their combination in 12 healthy volunteers with 2 weeks washout period between phases. The effects of clopidogrel (300 mg loading dose and 75 mg od) in 8 patients undergoing intracoronary stent implantation were assessed with blood sampling prior to and 4-7 days after clopidogrel, with addition of AR-C69931MX 100 nM in vitro before and after clopidogrel administration.
Results: In the healthy volunteer study, ADP (30 μM) induced significant aggregation, P-selectin expression, platelet-monocyte and platelet-neutrophil conjugate formation that were all inhibited by clopidogrel ($p<0.01$ all parameters) but not by aspirin e.g. platelet-monocyte % conjugates 89.1 ± 1.8 before treatment, 59.3 ± 5.2 clopidogrel, 89.6 ± 2.3 aspirin, 53.0 ± 5.2 clopidogrel + aspirin. The same inhibitory effects of clopidogrel were seen in the patient study. AR-C69931MX yielded greater inhibition of aggregation and P-selectin expression ($p<0.05$) than clopidogrel. AR-C69931MX significantly added to the inhibitory effect of clopidogrel on platelet-monocyte conjugate formation (platelet-monocyte % conjugates: before clopidogrel 96.3 ± 0.6, before + AR-C69931MX 63.5 ± 7.0, clopidogrel 80.3 ± 5.1, clopidogrel + AR-C69931MX 61.2 ± 7.2, $p<0.01$).
Conclusions: Inhibition of platelet-leukocyte conjugate formation, via inhibition of platelet P-selectin expression, by clopidogrel and AR-C69931MX may confer therapeutic anti-inflammatory effects in the management of patients with ischaemic heart disease. The greater effects of AR-C69931MX compared to clopidogrel support further clinical trials of this agent.

P3690 The EARLY platelet substudy

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Background: Receptors other than GPIIb/IIIa may mediate leukocyte-platelet-endothelial interactions that obstruct the microvasculature in acute coronary syndromes (ACS) and cause microinfarcts. The effect of eptifibatide on these receptors was investigated in a substudy of the EARLY trial.
Methods: Patients received early(in the Emergency Department, n=27) or late (12-24 hours, n=28) eptifibatide. Ten platelet receptors by flow cytometry and platelet aggregation were measured serially at baseline, and at 3,6,12 and 24 hours after randomization.
Results: Demographics were similar, except that late patients were older. No significant differences were seen in either group for CD 31, CD 63, CD 107a, CD107b, CD 41 (GPIIb/IIIa expression), CD 62p or platelet-leukocyte aggregate formation. PAC-1 (GPIIb/IIIa activity), CD 51/61 (vitronectin receptor)and CD 42b (GPIb)were inhibited by eptifibatide ($p<.05$). See table.

Early data

	ADP (%)		PAC-1 (MFI)	
	Early	Late	Early	Late
B-L	72± 20	80±12	5.8±9	5.5±1.2
3H	7±9*	58±21+	2.2±4*	4.9±2.1+
6H	4±9*	63 ±23+	2.4±1.1*	4.4±1.6+
12H	8±17*	66±26+	2.6±1.1*	3.7±7
24H	30±33*	9±16+*	2.3±4*	3.1±1.4*
	CD 51/61 (MFI)		CD42b (MFI)	
	Early	Late	Early	Late
B-L	11.9±4.4	11.5±5.5	207±60	126±70+
3H	5.9±3.2*	10.8±3.1+	121±40*	140±93
6H	5.6±2.3*	12.4±3.3+	135±73*	117±59
12H	6.1±2.9*	12.9±3.0+	129±62*	155±42
24H	6.0±2.3*	6.2±2.3*	135±82*	107±59

ADP= aggregation by 10u mol ADP, MFI= mean fluorescence intensity, *$p<.05$ vs. baseline, + $p<.05$ between groups, B-L= baseline

Conclusion: 1) In the Emergency Department, early eptifibatide therpay rapidly and profoundly inhibits platelet aggregation. 2) The drug effect on platelet receptors appears limited not only to a reduction in GPIIb/IIIa activity, but also to CD 51/61 and CD 42b inhibition.

P3691 Evidence of platelet aspirin resistance acquisition after a long-term treatment

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Acetylsalicylic acid is the most commonly used antiplatelet drug in the prevention of atherothrombotic diseases. While the clinical efficacy of aspirin in acute coronary syndrome has been well established, chronic use of aspirin may be not efficacious in preventing cardiovascular events. Here we report for the first time that aspirin resistance is a phenomenon that can appear after a prolonged treatment with this drug. In 150 patients with atherothrombosis maximal percentage and the lag phase of Platelet Aggregation induced by collagen (2 microg/ml) and ADP (2 microM) was performed before and after 2, 6, 12, and 24 months of aspirin treatment were evaluated.
The lag-phase was unmodified in 21% of the patients at 2 and 6 months, in 36% at 12 months and 60% at 24 months compared to the baseline values.
Maximal aggregation was unmodified in 19% of the patients at 2 months, in 23% at 6 months, in 35% at 12 months and 51% at 24 months compared to the baseline values. ADP aggregation was unmodified in 27% of the patients at 2 months in 29% at 6 months, in 34% at 12 months and 53% at 24 months compared to the baseline values. In all patients the response to arachidonic acid was absent during aspirin treatment.
Treatment with ticlopidine (250 mg/die) did not show any change of platelet aggregation during two years of follow-up.
Taken together these data suggest that there are two types of aspirin resistance, one occurring early after aspirin ingestion, another later at least after 6 months of aspirin ingestion. These findings suggest the existence of multiple mechanisms causing aspirin resistance. In conclusion, we showed that prolonged aspirin treatment is associated with progressive restoring of platelet function. Identification of aspirin resistance may be useful to tailor individual therapy in patients with atherothrombosis.

P3692 R-PA and abciximab, r-PA, TNK-tPA and streptokinase: fibrinolytic and haemostatic alterations in myocardial infarction

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In order to reduce undesirable side-effects, newer thrombolytics should have a high fibrin-specificity. We investigated the effects of the regimen with half dose reteplase (r-PA) & the GpIIb/IIIa antagonist abciximab compared with full dose r-PA, tenecteplase (TNK-tPA) and streptokinase on systemic plasmin and coagulation activation markers (plasmin antiplasmin complexes (PAP), thrombin antithrombin-III (TAT)). 20 (pts.) with acute myocardial infarction had r-PA & abciximab, 18 pts. had r-PA, 10 pts. were given TNK-tPA and 26 pts. received streptokinase; control group: 75 healthy persons.

	0h	3h	6h	24h
PAP (μg/l), controls 349±29				
TNK-tPA	646±233	8136±1150*#	6489±284*	607±72#
R-PA/abcix.	513±76	14914±2667*#	11883±2257*	398±63#
R-PA	574±86	25204±3048*¶	14870±2382*	429±90#
Streptokinase	526±97	29457±4043*	10255±1443*	6404±1165*
TAT (μg/l), controls 3.0±0.2				
TNK-tPA	10.6±6.4	10.5±4.2*#	5.6±1.0#	6.1±0.8
R-PA/abcix.	7.6±3.1	10.0±2.4*#	8.7±3.1#	7.2±1.8
R-PA	6.0±1.5	12.0±4.7*#	5.0±1.1#	7.2±2.3
Streptokinase	13.0±3.7*	49.8±16.8*	49.9±17.0*	23.9±7.1*

*: p<0.05 vs. controls; #: p<0.05 vs. r-PA, ¶: p<0.05 vs. TNK-tPA

The TNK-tPA group had the highest, the streptokinase group the lowest in vivo fibrin-specificity. R-PA & abciximab caused a lower systemic procoagulatory state vs. r-PA alone, however, these effects were more marked compared with TNK-tPA.

P3693 Thrombolytic therapy prior to coronary thrombectomy using the rescue PT catheter in acute myocardial infarction

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Background: Pharmacological thrombolytic therapy is an established method in the management of acute myocardial infarction with ST-segment elevation. There are, however, no reports showing the safety and efficacy of this approach in conjunction with direct, catheter-based coronary thrombus removal.
Methods and Results: In 42 consecutive pts (mean age 56±9 years, 33 male, 9 female) with acute ST-segment elevation myocardial infarction the Rescue percutaneous thrombectomy (RPT) system (Boston Scientific) was applied to remove fresh (< 12 hours) coronary thrombus. Among those pts, 14 were treated with thrombolytic agents (1.5-2 mio IE streptokinase n=6, 10 U reteplase n=8) prior to the intervention (L+). Their clinical characteristics including age, gender, "door-to-needle"-time and target vessel were similar to the remaining 28 pts without thrombolytic pretreatment (L-). Initial TIMI > 0 flow was observed in 8/14 L+ pts (57%), as opposed to 6/28 L- pts (21%, p=.021). This resulted in a shorter X-ray (12±7 vs 19±8 min, p=.025) and also a trend towards shorter total procedure duration (60±30 vs 77±43 min, p=.145) in L+ pts. After thrombosuction TIMI 2 or 3 flow was present in 8/28 (28%) and 19/28 L- pts (68%), and in 3/14 (21%) and 9/14 L+ pts (64%), respectively (p=ns). There were no procedure related complications in both groups. L+ pts had a shorter hospital stay (3.7±2.7 days) than L- pts (6.7±6.5 days, p=.044).
Conclusions: Thrombolytic therapy prior to catheter-based coronary thrombus removal appears to be safe and effective. A larger prospective, randomized trial assessing this approach seems warranted.

P3694 Safety and efficacy of a new Streptokinase regimen (0.75 MU/10 min) in combination with Enoxaparin in acute myocardial infarction

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Background: Recent data suggested a similar efficacy of the combination between the standard Streptokinase (SK) regimen (1.5 m.u./60 min.) and Heparin (H) with the one between the Standard SK and Enoxaparin (Enox) in patients (pts) with acute myocardial infarction (AMI).
Objective: Safety and efficacy of a new SK regimen (0.75 M.U. infused in 10 min.) in combination with Enox has been compared to the one of the classical combination Standard SK and H.
Methods: A group of 302 pts admitted within the first 6 hours after the onset of the chest pain revealing AMI was divided in two subgroups according to the SK regimen. In subgroup A (147 pts.) a dose of 0.75 MU was infused in 10 min. The first bolus was followed after 50 min. by a new dose of 0.75 MU/10 min. only if no bed-side signs of coronary reperfusion (CR) have been detected These pts. also received Enox i.v. 40 mg. either before or immediately after the end of the first SK bolus and 1 mg/kg every 12 hours for the next 48-96 hours. In subgroup B (155 pts.) the classical SK regimen was used. In these pts. an infusion of 1000 iu/hour of H started immediately after the SK administration and lasted for the next 48-96 hours. All pts. received aspirin. Three noninvasive CR criteria have been used: 1.Rapid cessation of the chest pain. 2.Rapid decreasing of the sum of the ST segment elevations by more than 50% from the initial value. 3.Rapid increasing of the CK and CK-MB with a peak within the first 12 hrs.
Results: The ratio of the CR was 75.5% in subgroup A, significantly higher that the one of 61.9% registered in subgroup B (p=0.016). The in-hospital mortality was 7.48% in subgroup A and 12.25% in subgroup B. Neither stroke nor other major haemoragical events were registered in both subgroups. Symptomatic hypotension was more frequent in patients belonging to the A subgroup (34.6%) as compared to the B subgroup (23.8%)(p>0.05). However hypotension proved to be transient and well controlled in all patients.
Conclusions: Combination between SK 0.75 MU/10 min. plus Enox is safe and leads toward a significant higher ratio of CR and a lower in-hospital mortality as compared to the classical SK regimen plus H.

P3695 Early posthrombolysis lesion pattern, coronary flow and myocardial perfusion in ST elevated infarcted patients: results from the GRACIA trial

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Objective: We analysed basal angiographic data of infarcted and thrombolysed patients included in the interventional arm of the GRACIA trial. Purposes of this subanalysis were: 1) To assess coronary flow and myocardial blush following TIMI classification; 2) to assess the angiographic characteristics of the culprit lesion within 6 to 24 hours after trhombolysis with rt-PA and; 3) to investigate clinical predictors of effective flow after thrombolysis.
Methods: The GRACIA trial included 500 pts randomly assigned to angiography and intervention within 6-24 hours of thrombolysis, or conservative posthrombolysis ischemia-guided approach. We studied the angiographic data from the 250 interventional patients (age: 60±12 years, 87% female), which were obtained 17±6 hours (range 6 to 24 hours) after thrombolysis. Infarction were located in the inferior wall in 57% of patients. The delay between onset of symptoms and thrombolysis was 3.0±1.8 hours. Angiographic evaluation was carried out by an independent core laboratory.
Results: Location of the culprit lesion was: left descending artery: 38%; right coronary artery: 47%; circumflex: 15%; left main: 0.4%. At the time of angiography only 11% of arteries had TIMI 0-I flow and the remaining 89% of patients had TIMI flow III (73%) or II (17%). The blush score was grade 0 in the majority of the arteries (81%), grade 1 in 2 arteries (1%), grade 2 in 3 arteries (1%) and 3 grade in the remaining 17% of arteries. Diameter stenosis of the culprit lesions was 83±18%. Complex morphology was found in 38% culprit lesions. Only 20% of culprit lesions had angiographic evidence of thrombus. Multivariate analysis (logistic regression) of clinical variables showed two independent predictors of operative flow (TIMI II or III): a) the infarct location in the inferior wall (OR: 1.6 CI 95%: 1.01-2.49, p=0.04), and b) the presence of multivessel disease (OR 0.63, CI 95% 0.41-0.98, p= 0.04).
Conclusions: 1) Most pts with AMI had a good myocardial perfusion and effective coronary flow in the angiography performed 6 to 24 hours after thrombolysis; 2) The probability TIMI flow II or III is 60% higher in patients with inferior AMI; 3) the probability of effective flow is 40% lower in pts with multivessel disease.

P3696 Transcutaneous ultrasound enhances coronary thrombolysis. The first human pilot study

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Background: Thrombolysis efficacy is limited by moderate patency rates and increased bleeding risk. Animal studies using the combination of transcutaneous low frequency ultrasound and thrombolysis have shown improved patency over thrombolysis alone.
Objective: To assess the safety and feasibility of noninvasive, transcutaneous low frequency ultrasound (Timi3 Systems, Inc, Santa Clara, CA) as adjunctive treatment to thrombolytic therapy for patients with acute myocardial infarction (MI).
Methods: Patients presenting with ST elevation MI within 6 hours of symptom onset, without contraindications for thrombolytic therapy, were enrolled in the study. Patients were treated with reteplase (n=15) or tenecteplase (n=10) and 60 minutes of low-frequency transcutaneous ultrasound applied on the midsternal area within 8±12 min after initiation of fibrinolysis. The primary efficacy endpoint was TIMI grade flow at 90 minutes in the infarct related artery (IRA). All patients were followed for 30 days.
Results: Of the 25 patients enrolled between December 2000 and August 2001, 24 were treated with 60 min of ultrasound. Mean age was 57±10 years; prior MI was present in 4 (16%) patients. Symptom onset to fibrinolytic administration was 193±82 min. The IRA was the LAD in 9 (36%) patients, the LCx in 1 (4%) patient, and the RCA in 15 (60%) with a mean residual stenosis of 92%. At 91±14 minutes, TIMI grade 3 flow was present in 16 (64%) patients, TIMI grade 2 in 5 (20%). None of the patients had TIMI grade 0. ST segment deviation resolution at 90 min after ultrasound in combination with thrombolysis was greater than 50% in 67% of patients. Post-angiography PCI was performed in 13 patients. There were no strokes, reinfarctions or deaths at 30-day follow-up. No major adverse events were associated with adjunctive transcutaneous ultrasound therapy.
Conclusion: Transcutaneous ultrasound therapy and standard thrombolysis are feasible and safe in MI patients. A randomized clinical trial is under way to further assess the efficacy of this novel, non-invasive, non-pharmacologic approach to augmenting thrombolytic therapy.

P3697 Impact of reocclusion on 5-year survival and reinfarction following fibrinolytic therapy: long-term follow-up of the APRICOT-1 trial

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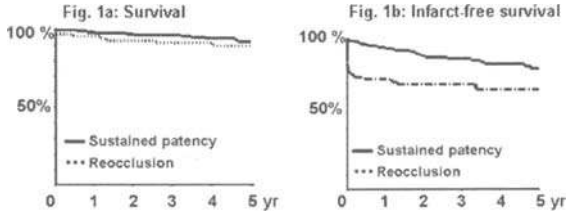
Background: In the first three months after successful fibrinolytic therapy, reocclusion has been shown to occur in about 30% of patients. Whereas reocclusion within a week after demonstrated patency has been associated with a twofold increased risk of mortality, the prognostic impact of reocclusion after the acute phase remains to be determined.
Methods: In the APRICOT-1 trial 248 patients < 71 years had fibrinolysis for acute myocardial infarction within 4 hours of symptom onset and a patent infarct artery at angiography < 48 hours. Follow-up angiography and ventriculography was scheduled at three months. Death and reinfarction were recorded using medical charts, telephone contact with the general physician and information from municipal registries.
Results: Reocclusion was observed in 71 patients (29%). Left ventricular ejection fraction increased from 51±10% to 55±11% in patients with sustained patency ($p < 0.01$); in patients with reocclusion the change in ejection fraction was -1.0±1.8% (p=ns). Mean clinical follow-up was 4.3±1.2 years. At five years, survival was 90% for patients with reocclusion compared to 92% for patients with a patent artery at follow-up angiography (fig.1a, p=ns). Death and reinfarction rates were 34% and 20%, respectively (fig.1b, $p < 0.01$).
Conclusion: After demonstrated coronary patency following fibrinolysis for acute ST-elevation myocardial infarction, patients who survived the first 48 hours had an excellent 5-year prognosis. Although reocclusion was associated with a higher risk for reinfarction and impaired left ventricular contractile recovery, the potential adverse impact on long-term survival could not be demonstrated.



P3698 Platelet-monocyte-endothelium interactions: aspects of r-PA versus r-PA and abciximab in acute myocardial infarction

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Alterations of the fibrinolytic/haemostatic system as well as the involvement of platelets, leukocytes and endothelial cells have been described in acute myocardial infarction. Newer regimen with a thrombolytic and a GpIIb/IIIa antagonist additionally influence these systems.
We investigated the effects of a new combined regimen with $\frac{1}{2}$ dose reteplase (r-PA) and the GpIIb/IIIa antagonist abciximab versus full dose r-PA on CD40, CD40 ligand (CD40L) and CD42b on monocytes in a substudy of GUSTO V; controls: 28 healthy persons.

	0h	90min.	3h	12h	16h
CD40 (monocytes, %); controls 68±2.7					
R-PA	72±4.2	74±3.5	72±4.3	71±4.0	81±2.6
R-PA/abcix.	69±3.4	63±4.1	62±4.2*	74±4.1	73±3.6
CD40L (monocytes, %); controls 5.7±1.2					
R-PA	6.3±2.0	5.6±2.0	4.7±1.9	4.0±2.0	3.9±2.2
R-PA/abcix.	8.8±2.4	7.5±1.5	4.1±0.8#	6.7±2.0	6.1±2.0
CD42b (monocytes, %); controls 44.2±4.8					
R-PA	39.5±7.8	32.6±7.3	25.5±6.1	28.0±9.0	29.3±8.5
R-PA/abcix.	38.0±6.4	34.0±6.5	25.4±4.6¶	39.5±7.7	35.0±6.6

decrease 0h/3h: *: p=0.078, #: p=0.025, ¶: p=0.005

The r-PA/abciximab group showed a marked decrease of CD40-, CD40L- and CD42b-positive monocytes in contrast to the r-PA group. This could be an indicator for more benefical effects of the combined regimen on platelet-induced monocyte activation, platelet-monocyte-endothelial adhesion and on CD40/CD40L associated procoagulatory, proinflammatory and proadhesive effects by monocytes.

P3699 A comparison of efficacy and safety between three streptokinase regimens and front loaded Alteplase in patients with acute myocardial infarction

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Objective: In a prospective study we compared the safety and efficacy of the front loaded Alteplase (tPA) regimen (100 mg./90 min) to the one of three Streptokinase (SK) regimens: 1. Infusion of 1.5 M.U./60 min (the SK1.5/60 regimen). 2. Infusion of 1.5 MU/20 min (the SK1.5/20 regimen). 3. Bolus of 0.75 M.U./10 min followed by a new bolus of 0.75 M.U./10 min. after 50-60 min. only if no bed side signs of coronary reperfusion (CR) have been detected (the SK 0.75/10 regimen).
Methods: A group of 440 patients (pts.) admitted within the first 6 hours after the onset of the chest pain revealing acute myocardial infarction (AMI) have been divided in 4 subgroups according to the thrombolytic regimen used: the tPA subgroup (82 pts.); the SK1.5/60 subgroup (121 pts.); the SK 1.5/20 min. subgroup (125 pts) and the SK 0.75 MU/10 min. subgroup (112 pts.). All pts also received heparin (1000 i.u./hour, 48-72 hours) and aspirin.. Three noninvasive CR criteria have been used: 1.Rapid cessation of the chest pain. 2.Rapid decreasing of the ST segment elevation by more than 50% from the initial value. 3.Rapid increasing of the CK and CK-MB with a peak within the first 12 hrs. The incidence of haemorrhagic events, the ratio of CR, and the in hospital mortality were evaluated.
Results: The ratios of the CR were 74.39% in the tPA subgroup, 75.2% in the SK1.5/20 and 75.0% in the SK0.75/10 sbgroup. These ratios proved to be practically equal each other but all were significant higher that the one of 59.5% registered in the SK1.5/60 min. subgroup. (p=0.031, 0.009 and 0.012, respectively). The in hospital mortality was 7.3% in the tPA subgroup, 7.2% in the SK1.5/20, 8.03% in the SK0.75/10 and 12.39% in the SK1.5/60. No significance difference has been registered among the 4 subgroups. One patient in the tPA subgroup and 1 patient in the SK1.5/60 subgroup had signs of ischemic stroke. The incidence of the major haemorrhagic events were 2.4% in the tPA subgroup, 3.3% in the 1.5/60, 3.2% in the SK1.5/20 and 2.6% in the SK0.75/10 (non-significant differences)
Conclusions: Our data suggest that two accelerated SK regimens (SK1.5/20 and 0.75/10) are equally efficient and safe as compared to the front loaded tPA regimen. The classical SK1.5/60 regimen seems to be the weakest one among the three SK regimens tested in this study.

P3700 A lytic test for determination of resistance to streptokinase predicts 30-day survival in patients treated with streptokinase for acute myocardial infarction

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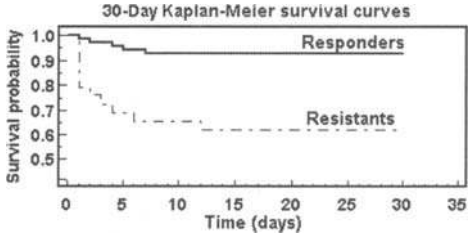
Background: Streptokinase (SK) remains world-widely used because of its low cost. The survival benefit obtained with SK is not optimal in AMI patients with prior exposure to streptococcal antigen by infection or previous SK treatment. The high anti-SK antibody titers in these patients are neutralizing SK, hamper the thrombolytic response and probably clinical efficacy. The prevalence of SK resistance in candidates for thrombolytic treatment is 9-28% depending on the region. Identification of patients who are potentially resistant to SK before therapy would contribute to prompt selection of an alternative reperfusion strategy. A recent thrombolytic assessment system (TAS) furnished a lytic test for rapid screening for SK resistance.
Objective: To evaluate the predictive value of this lytic test, applied to patients with AMI before treatment with a standard dose of SK, on 30-day survival.
Methods: Hundred consecutive AMI patients were screened with the TAS SK resistance test before the administration of SK, test results were blinded. Each patient, whom was discharged alive, was contacted by telephone to ascertain vital status at 30 days.
Results: There were 71 patients screened as responders and 29 as resistants. Final follow-up was 99%. 30-day survival rate was in favor of responders (94.4%) over resistants (61.9%, p<0.001). The resistants group was older (p=0.004). Age adjusment was done using Cox's regression analysis, survival rate remained in favor of responders (p=0.027); hazard ratio: 3.94 (95% CI 1.17 - 13.27).



Survival curves.

Conclusion: The 30-day results showed a worse outcome for patients screened to be resistants, and demonstrate that pre-therapeutic determination of resistance to streptokinase can significantly contribute to a better management of patients with AMI.

P3701 Neutralization of the anticoagulant effect of fondaparinux by recombinant activated factor VII in healthy male volunteers

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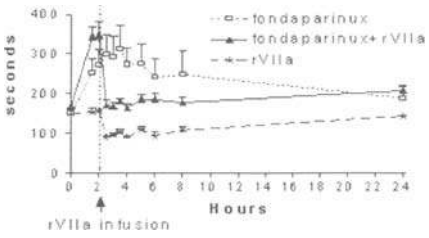
Background: Fondaparinux sodium (Arixtra®), a synthetic selective factor Xa inhibitor, has proved beneficial for treatment of thrombotic disorders. In the context of the use of every anticoagulant drug, bleeding may occur. Therefore we tested the efficacy of recombinant activated factor VII (rVIIa, NovoSeven®) in neutralizing the anticoagulant effect induced by a high dose of fondaparinux in healthy volunteers.
Methods: The study was a randomized, placebo-controlled, three-parallel group trial. Male volunteers were to receive a single subcutaneous administration of either fondaparinux (10 mg) followed by an intravenous bolus injection of rVIIa (90 μg/kg, n=8); or fondaparinux followed by an intravenous bolus injection of placebo (n=4); or placebo followed by rVIIa (n=4). Placebo rVIIa and rVIIa were given in a double-blind fashion two hours after fondaparinux or placebo.
Results: Administration of rVIIa after pretreatment with fondaparinux prevented the decrease in thrombin generation marker prothrombin fragment 1.2 (F1+2) as observed after fondaparinux administration. These in vivo data were supported by the results of two ex vivo thrombin generation tests. The injection with rVIIa, after the treatment with fondaparinux, resulted in a rapid and marked thrombin generation, reflected by the reduction of the time to fibrin polymerization in the thrombin generation assay (figure) and by the induction of endogenous thrombin potential (ETP).
Conclusion: In this trial the inhibition of thrombin generation induced by fondaparinux was rapidly and significantly counteracted by rFVIIa. The overall results suggest that rVIIa is an effective and safe candidate as an antidote for fondaparinux.



Thrombin generation time

P3702 Angiographic and clinical outcomes after coronary artery stenting with glycoprotein IIb/IIIa inhibitors – Is the gender gap closing?

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Background: Women undergoing percutaneous coronary interventions (PCI) are generally considered at higher early risk compared to men. However, it is unknown whether this risk profile persists also when glycoprotein (GP) IIb/IIIa inhibitors are used during coronary artery stenting.
Methods: We identified 1215 concecutive patients who received GP IIb/IIIa inhibitors during 1852 coronary artery stent implantation procedures. Of these, 322 (26.5%) were women (488 procedures).
Results: Women had similar rates of in-hospital myocardial infarction (MI) (0.9% vs. 0.56, p=0.48) and target vessel revascularization (TVR) (0% vs. 0.22%, p=0.72) compared to men. There were no procedural or in-hospital deaths. No statistically significant differences were observed in bleeding and major vascular complications. One-month major adverse cardiac event (MACE) rate was also similar in both women and men (4.0% vs. 3.3%, p=0.5).

Procedural and in-hospital complications

	Female	Male	P value
Procedures	488	1364	
Angiographic success	488 (100%)	1354 (99.26%)	0.06
Acute stent thrombosis	1 (0.2%)	10 (0.7%)	0.20
Subacute thrombosis	5 (1%)	11 (0.8%)	0.65
Procedural MI	3 (0.93%)	5 (0.56%)	0.48
Q-wave MI	2 (0.62%)	1 (0.11%)	0.11
Non-Q-wave MI	1 (0.31%)	4 (0.44%)	0.10
Procedural CABG	0 (0%)	2 (0.22%)	0.72
Bleeding complications	0 (0%)	3 (0.33%)	0.29
Vascular complications	4 (1.2%)	6 (0.67%)	0.33

Conclusions: In-hospital and one-month outcomes of women undergoing PCI with GPIIb/IIIa inhibitors are similar to those of men.

P3703 Is the clopidogrel effect by patients treated with statins diminished? A flow cytometric evaluation of a possible interaction

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The thrombocyte function inhibitor clopidogrel is transduced by the cytochrom P450 3A4 into his active metabolite. The same isotype is also responsible for the metabolization of most statins like atorvastatin. We try to answer the question if the clopidogrel linked effect in the thrombocyte function is diminished under a treatment with some statins.
Citrated blood is drawn from patients after stenting (n=20) without a relevant comedication, from patients with atorvastatin medication (n=20) and from patients treated with other statins (pravastatin, fluvastatin) not metabolized via CYP 3A4 (n=10) just before the clopidogrel medication started, 5h after the loading dose (300mg) was taken and 48h later (75mg/d). Between these groups we also separate long term and short term statin treatment.
In not fixed centrifugated blood we examined the CD62P-(p-selectin)-expression of ADP-stimulated (1, 3, 10, 30, 100uM ADP) thrombocytes with a flow cytometer (Beckman-Coulter Epics).
For this three evaluated groups we found till now (n=15) after 48h clopidogrel treatment for the relative inhibition of the CD62P-expression after ADP-Stimulation (with 10, 30, 100uM) following results: clopidogrel-monotherapy 75.4%/74.9%/74.1%, atorvastatin 66.7%/65.4%/64.1% and statins like pravastatin 74.9%/75.0%/79.6%.
It seems that - at least in a special group of patients - the comedication with some statins (like atorvastatin) reduces the effect of clopidogrel.

P3704 Clot disruption without thrombolytic agent – Combination of low frequency ultrasound and levovist

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Background: We have reported that ultrasound (USD) thrombolysis is effective enough to recanalize the acute thrombotic occlusion in vivo. However, the combined thrombolytic effect of Levovist and USD has not been compared with that of the tissue plasminogen activator. We investigated the rate of clot weight reduction in vitro to evaluate the enhancing effect of Levovist with high and low frequency USD. Methods: Fresh whole blood clots from normal volunteers were placed in a test tube containing 2ml fresh human plasma and simulated clinical dosage of monteplase or Levovist at 37C. Clots mixed with monteplase were incubated for 30 minutes and clots mixed with Levovist were exposed to 1MHz or 27kHz continuous wave USD for 30 minutes and 5 minutes in a bath filled with degassed water. Results: After 30minutes of 1 MHz USD exposure with Levovist, only 11.3±5.4% of clot weight reduction was observed. However, 5 minutes of 27 kHz USD exposure in combination with Levovist resulted in 28.6±5.2% of clot weight reduction, which was similar to that of 30 minutes incubation with monteplase (31.6±11.8%). Conclusion: Combined treatment with Levovist and low frequency (27 kHz) ultrasound showed similar degree of thrombolysis to tissue-plasminogen activator in a shorter period of time (5 minutes vs. 30 minutes).

P3705 ASS, beta blocker and angiotensin-converting enzyme inhibitors as an initial therapy for acute myocardial infarction: results from the Berlin myocardial infarction registry

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Early reperfusion therapy (RT) improves the prognosis of patients (pts) after acute myocardial infarction (AMI). But how important is the early initial therapy with Aspirin (ASS), Beta Blockers (BB) and ACE inhibitors (ACE)?
Method: Using data from the Berlin Myocardial Infarction Registry (BMIR) on 2945 pts with AMI in 1999/2000, the number and mode of performed reperfusion therapy (RT) and the kind of initial medical therapy with ASS, BB and ACE as well as their combination and their influence on hospital mortality (HM) were examined. Adjustment was made for statistically relevant characteristics like age, gender, congestive heart failure and co-morbidity.
Results: RT was performed in 1741 pts (59%). Unadjusted HM in this group of pts was 8,6% (150). The unadjusted HM was significant higher if RT was not performed (19,3%/232 pts; p<0,05). 2703 pts (91,8%) were treated initially with ASS, 67,5% with BB and 50% with ACE. 37,4% received the combination of all the three agents. Unadjusted HM in this group was 5,9%.
Results of a multivariate regression analysis on influence of initial therapy on HM showed that improved survival of pts receiving RT was associated with the initial therapy of BB (OR=0,27, 95% CI: 0,15-0,5), ACE (OR=0,44, 95% CI: 0,2–0,7) and the combination therapy (OR=0,44, 95% CI:0,23-0,85). Survival of pts without RT was also improved with the therapy with ASS (OR=0,36, 95% CI:0,21-0,6), BB (OR=0,46, 95%CI:0,32-0,68), ACE (OR=0,51, 95% CI:0,35-0,75) and their combination (OR=0,52, 95% CI:0,33-0,82).
Conclusion: The initial therapy with ASS, BB, ACE reduces HM significantly. This reduction is independent of early reperfusions therapy. Combination therapy is used only in one third of pts with AMI. These data underline the important role of the concomitant medication in pts with AMI.

P3706 Reduction of hospital mortality in patients with ST-segment elevation myocardial infarction receiving IIb/IIIa antagonists: results of the ACOS-registry

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Background: The benefitial effect of IIb/IIIa-recpetor antagonists (IIb/IIIa) has been proven in randomised trials on acute coronary syndromes (ACS). Little data exist on the frequency of IIb/IIIa use and its influence on outcome of patients with acute ST-elevation myocardial infarction (STEMI) in clinical practice.
Methods: Since June 2000 consecutive patients (pts) with ACS have been enrolled into the ACOS-Registry (Acute Coronary Syndrome, 154 hospitals) in Germany. We analysed the prospective data of STEMI-pts with and without treatment with IIb/IIIa to identify the impact of this treatment on hospital outcome.
Results: Out of 9065 consecutive pts with ACS, 4205 (46%) presented with STEMI, 1520 of these pts (36%) were treated with IIb/IIIa. Determinants for the use of IIb/IIIa in STEMI were prehospital delay < 4 hours (OR 1.31, 1.07-1.62) and the performance of primary PTCA (OR 5.59, 3.29-6.40). Prior STEMI or concomitant diseases (hypertension, diabetes) did not influence the decision. STEMI pts treated with IIb/IIIa were younger and already had received prior PTCA more often than pts who were not treated with IIb/IIIa.

Outcome dependent on treatment

	STEMI with IIb/IIIa	STEMI without IIb/IIIa
Age (years)	63	66
Prior PTCA	8,2%	5,3%
Hypercholesteremia	48,1%	42,6%
Diabetes	21,8%	26,9%
Thrombolysis	5,0%	29,8%
PTCA	60,0%	22,9%
Stent (relative to PTCA)	81,8%	74,6%
Hospital mortality	6,2%	11,2%

p<0,001 for all parameters

After adjusting for differences in baseline characteristics and acute reperfusion therapy, the use of IIb/IIIa in STEMI pts was associated with a 33% reduction of hospital mortality (OR 0.67, 0.43-0.92). The use of IIb/IIIa decreased the length of hospital stay (OR 0.65; 0.53-0.80)
Conclusion: The use of IIb/IIIa in acute STEMI was associated with an additional 33% reduction of hospital mortality on top of the benefit of acute reperfusion therapy and with a shorter hospital stay.

P3707 Tissue factor transfer to platelets in acute myocardial infarction

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Background: Current data indicate that acute myocardial infarction (AMI) results from local plaque rupture and subsequent platelet adhesion/aggregation in the course of a systemic inflammatory state. One of the known proteins associated with this condition is tissue factor (TF), a potent initiator of the coagulation cascade. Because in vitro activated platelets have been shown to take up TF from leukocytes, we analyzed the TF content of circulating platelets from patients with AMI.
Methods and Results: Venous blood from 12 AMI patients with <6 hours of chest pain was collected in the catheter laboratory prior to administration of glycoprotein IIb/IIIa antagonists. Blood samples from 6 patients with normal coronary arteries served as controls. TF antigen levels associated with 10e+9 washed and freeze-thawed platelets per ml were significantly higher in AMI patients (22.9±12.6pg/ml) than in controls (3.7±5.9pg/ml, p=0.003). In contrast, TF antigen levels in platelet poor plasma of AMI patients (141.3±139.0pg/ml) were not different from controls (111.1±67.50pg/ml, p=0.488). Immunoelectronmicroscopy utilizing a monoclonal antibody directed against TF allowed the localization of TF to the alpha-granules. No TF mRNA was detectable in platelets, while megakaryocytic cell lines expressed various amounts of TF mRNA.
Conclusion: Our data show that platelets incorporate TF in vivo, thereby potentially quenching TF molecules from the circulation. These findings suggest a novel role for platelets in AMI.

DRUG EFFECTS ON BLOOD COAGULATION AND VESSELS

P3708 Simvastatin inhibits leukocyte-endothelial cell interactions during septicemia by staphylococcus aureus alpha-toxin

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Simvastatin, a HMG-CoA reductase inhibitor (statins) has been shown to lower serum cholesterol-levels in clinical use. Moreover, statins exert beneficial effects in vascular diseases, where leukocyte rolling, adherence, and subsequent transmigration through the endothelial wall in the microcirculation are key steps in the inflammatory response. The aim of the study was to determine if pretreatment with simvastatin attenuates staphylococcus aureus-alpha toxin induced increase in leukocyte-endothelial interactions during exotoxemia. The effects of simvastatin on leukocyte-endothelial cell interactions were observed by intravital microscopy in the rat mesenteric microcirculation. Simvastatin (50 or 100μg/KG) was administered 18h before study. Acute endothelial dysfunction of the mesenteric microcirculation was induced by bolus administration of 40 μg/kg staphylococcus aureus alpha toxin. Exotoxemia induced by staphylococcus aureus alpha-toxin resulted in a significant and time-dependent increase in leukocyte rolling, leukocyte adherence, transmigration of leukocytes, and P-selectin expression on the vascular endothelium compared to control rats. In contrast, pretreatment with simvastatin significantly inhibited inflammatory-induced leukocyte rolling from 70±12 to 18±5 cells/min ($p<0.01$) and adherence from 14±4 to 4±1.5 cells ($p<0.05$) along the venular endothelium of the rat mesentery. In addition, simvastatin pretreatment significantly inhibited transmigration of leukocytes from 10.5 ± 1.2 to 3.5 ± 0.8 ($p<0.05$) cells through the microvascular endothelial wall. Similarly, P-selectin-neutralizing monoclonal antibody significantly inhibited these inflammatory interactions. Immunohistochemical detection of endothelial cell adhesion molecul P-selectin showed a 50% decrease in endothelial cell surface expression following simvastatin pretreatment and stimulation with staphylococcus aureus alpha-toxin.
These results clearly demonstrate that simvastatin potently ameliorates exotoxin-induced leukocyte-endothelial cell interactions associated with sepsis, or endocarditis in clinically relevant doses. Statin treatment may have a therapeutic role in attenuation of vascular activation and injury under exotoxin challenge.

P3709 Platelet function varies according to body mass index in patients undergoing percutaneous coronary intervention. Should clopidogrel loading-dose be weight adjusted?

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A 300 mg loading-dose regimen of clopidogrel at intervention time is widely used as an adjunct antithrombotic therapy to reduce the early risk of acute coronary thrombosis following coronary stent implantation (STI). At difference of other drugs used during STI, such as heparin and GP IIb/IIIa inhibitors, loading-dose of clopidogrel is not weight adjusted and few data are available on which is the most effective loading-dose regimen. Methods: To assess whether platelet response to STI may be influenced by weight, we studied 31 consecutive pts undergoing STI. In all pts we assessed body mass index (BMI) determined as weight/height^2 (kg/m^2). All pts were on treatment with aspirin (100 mg/day) and received a 300 mg loading-dose of clopidogrel at intervention time. During intervention 100IU/kg of heparin was administered. Pts receiving GP IIb/IIIa inhibitors were excluded. Platelet function was evaluated as percentage of platelet aggregation (%PA) upon stimuli with ADP (6μM) and collagen (6μg/mL) at baseline and 24 hrs after intervention using light transmittance aggregometry. According to the %PA upon 6μM ADP stimuli 24 hrs after STI, pts were divided into two groups: G1 (%PA >30%) and G2 (%PA <30%). Cut-off value of 30% was the median value of our study population and it is a widely used cut-off clinical value to assess platelet inhibition. Time point of 24 hrs is crucial for early coronary thrombosis and at this time full effect of loading-dose of clopidogrel should be observed. Results (mean±SD): G1 and G2 were composed of 13 (10 men; age:63±7y) and 18 (17 men; age:62±11y) pts, respectively. %PA upon ADP stimuli 24 hrs after STI was 52,92±16,8% in G1 and 18,67±7,6% in G2 ($p<0.001$). G1 presented a greater platelet aggregation than G2 upon stimuli with collagen 24 hrs after STI (55,05±26,34% vs 35,88±20,91%; p=0.032). No differences in platelet aggregation with ADP (54,76±24% vs 44,91±11,24%; p=0.19) or with collagen (47,10±16,83% vs 42,39±16,32%; p=0.44) were observed at baseline between G1 and G2. G1 pts were characterized by a greater BMI than G2 pts (28,14±2,9 kg/m^2 vs 25,8±3,2 kg/m^2; p=0.048). No difference in platelet count, clinical status, or risk factors between the two groups was observed. Conclusions: A lower platelet inhibition is observed 24 hours following STI in pts with a greater BMI. Such data suggest that pts with a higher BMI may need a greater loading-dose of clopidogrel than that commonly used in clinical practice. Assessment of platelet function in larger patient population using different loading-dose regimens are necessary to confirm this hypothesis.

P3710 Previous duration of out-hospital oral anticoagulation in patients hospitalised for haemorrhagic complications

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Studies which followed patients(pts) at oral anticoagulant therapy(OACT) had shown that frequency of hemorrhagic complications(HC) was highest in the first months of out-hospital OACT use.The aim of this study is to analyse previous duration of out-hospital OACT use in pts hospitalised for HC of this therapy. Material and method: We studied 78 pts hospitalised with the HC of OACT, at the Emergency Center in Belgrade, during 9 years(1989-98). The most frequent indications for out-hospital OACT use were mechanical prosthetic valve(in 38.5% pts), previous myocardial infarction(25.6%) and atrial fibrillation(17.9%). All studied pts were hospitalised because of the need for transfusion(Hgb less than 90g/l) and/or because of the value of INR at the onset of HC(mean INR was 10.5±8.7). The most frequent HC were skin and/or sceletal muscle hemathomas, gastrointestinal bleeding and hemathuria. The necessity of hospitalisation determined these HC as major bleeding events. All patients survived.
Results: Before the onset of HC, duration of out-hospital OACT use was from 2 days to 20 years, 2.5 years on average. The table shows frequencies of pts with different durations of out-hospital OACT use at the onset of HC.

	OACTuse timing										
	1st month	2nd month	3rd month	3rd-6th month	6th-12th month	2nd year	3rd year	3rd-5th year	5th-10th year	10th-15th year	15th-20th year
% Pts	23	17	3	8	8	13	8	8	9	1	4

Conclusion: In 78 pts with major HC of OACT, 23% of these HC occurred in the first month and 43% occurred in the first three months of out-hospital OACT use. This gets along with previous conclusions that HC are the most frequent at the begining of OACT use.

P3711 Selective serotonin reuptake inhibitors yield additional antiplatelet benefit in patients with heart failure treated with antecedent aspirin

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Background: Clinical depression has been identified as an independent risk factor for increased mortality in patients following acute coronary events. Enhanced platelet function has been suggested as the mechanism responsible for this adverse association, and participate in thrombotic events in patients with congestive heart failure (CHF). We sought to determine whether antecedent therapy with selective serotonin reuptake inhibitors (SSRI's) would affect platelet activity in such patients.
Methods: Eighty-eight patients with LVEF<40%, NYHA class II-IV were analyzed. Twenty-three patients (26%) were chronic SSRI users (SSRI+), and sixty-five patients were free from SSRI therapy (SSRI-) and served as internal controls. Demographics were similar between groups, except higher prevalence of diabetes, and incidence of previous myocardial infarction in the SSRI+ patients. SSRI+ group was treated more extensively. Platelet characteristics were assessed by aggregometry (conventional-, and whole blood); shear – induced activation, expression of 10 surface receptors, and formation of platelet-leukocyte conjugates by flow cytometry.
Results: SSRI+ patients exhibited a substantial decrease in platelet activity when compared with the SSRI- group which was significant for ADP- (p=0.001), and collagen-induced (p=0.02) aggregation, and the expression of PECAM-1 (p=0.03), GPIb (p=0.03), GP IIb/IIIa antigen (p=0.02), GP IIb/IIIa activity with PAC-1 (p=0.04), and P-selectin (p=0.02). Formation of platelet-leukocyte microparticles was also significantly reduced (p=0.01) in the SSRI+ group.
Conclusion: Despite chronic aspirin use, therapy with SSRI's yielda extra antiplatelet protection in patients with CHF. The inhibitory effects of SSRI's on platelet function observed in our study may be relevant to the association between treatment of depression and improved outcomes not only in patients with ischemic heart disease, but with CHF as well. Recognizing the universal antiplatelet properties of SSRI's, further clinical trials should elucidate the potential benefits of SSRI's in multiple vascular thrombotic conditions, including growing CHF population.

P3712 Effect of low molecular weight heparins (LMWH) use on inflammatory parameters in subacute phase of acute coronary syndromes

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Introduction: LMWH are widely used in acute coronary syndromes (ACS) treatment. Inflammatory response plays a significant role both in pathogenesis and prognosis of ACS while cytokines represent well accepted inflammatory markers. Aim of this study was to investigate possible beneficial effects of prolonged LMWH use on levels of inflammatory cytokines Interleukin-6 (IL-6), Interleukin-2 (IL-2) and Tumor Necrosis Factor á (TNFá) in subacute face of ACS.
Methods: Levels of IL-6, IL-2 and TNFá were measured in 30 pts with ACS at day of hospital discharge. After that study population was randomized in two groups of 15 pts each. In Group A LMWH home treatment continued for three weeks additionally to standard antiischaemic therapy (nadroparin, enoxaparin and dalteparin were used in lower dose to that usually used in acute face treatment) while in Group B only the standard therapy was given. At the end of the study levels of IL-6, IL-2 and TNFá were measured in all patients. Found values were compared to that at the beginning and comparison among two Groups was also performed. Compliance to LMWH therapy was checked by anti-Xá measurement.
Results: IL-6 was decreased in Group A (12.5 ± 7.0 vs 9.4 ± 4.5 pg/ml, p: NS) while it was increased in group B (10.3 ± 4.3 vs 14.8 ± 11.7, p: NS). It is important that IL-6 was decreased significantly in Group A as compared to Group B (-3.4 ± 7.8 vs 4.5 ± 10.5, p: 0.04). IL-2 was also decreased in Group A (0.268 ± 0.501 vs 0.122 ± 0.222 pg/ml, p: NS) while it was almost unchanged in Group B (0.090 ± 0.086 vs 0.090 ± 0.138, p: NS). No difference was found among two Groups (0.146 ± 0.538 vs 0.0002 ± 0.149, p: NS). TNFá was decreased in Group A (31.6 ± 56.2 vs 20.0 ± 18.3 pg/ml, p:NS) and it was decreased significantly in Group B (17.6 ± 38 vs 14.1 ± 2.9, p:0.005). However there was no difference among two Groups (-11.5 ± 38.3 vs −3.4 ± 4.0, p: NS). Mean anti-Xá activity in Group A at the end of the study was 0.57 ± 0.12 UI/ml (range 0.28-0.88 UI/ml)
Conclusions: Results of this study indicate a possible beneficial effect of prolonged LMWH use in subacute face of ACS on levels of inflammatory cytokines especially on IL-6, which is considered as the most important cytokine involved in ACS pathophysiology. However further investigation is needed to confirm if LMWH really have any anti-inflammatory effect beyond their anticoagulant effect.

P3713 Effects of antihypertensive monotherapy on plasma levels of pituitary adenylate cyclase activating polypeptide-38 in hypertensive subjects

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Hypertension is a major risk factor for cerebrovascular disease. Pituitary adenylate cyclase activating polypeptide-38 (PACAP-38) is a neuropeptide that produces dose-related, non-endothelial depended dilation of the cerebral vasculatore and neurotrophic-neuroprotective action in the ischemic neurons. The aim of this study was to evaluate the effect of different types of antihypertensive treatment on plasma levels of PACAP-38 in patients (pts) with mild to moderate essential hypertension.
Methods: Forty-nine pts with mild to moderate essential hypertension(HS), never treated before, with no evidence of any other acute or chronic health problem, were evaluated for plasma levels of PACAP-38 (measured by RIA) before and six months after antihypertensive treatment and compared to the corresponding levels of 10 age-,sex-,height- and weight- matched healthy volunteers [control group(CS)]. HS pts were divided in 4 groups (according to their treatment) matched for blood pressure(BP), left ventricular mass index (LVMI), total peripheral resistancies(TPRs), age, sex, weight and height: group A (14/49) was treated with moxonidine, group B (14/49) with perindoprilat, group C (12/49) with amlodipine and group D (9/49) with diltiazem, as monotherapy.
Results: All BP, LVMI, TPRs were found to be normalized after six months antihypertensive treatment in all groups. Comparing plasma levels of PACAP-38 (pg/ml), before and after therapy we found: group A, 20±7 vs. 51±13(P<0,05), group B, 25±7 vs. 25±10 (P=NS), group C, 25±9 vs. 46±20(P<0,05), group D, 23±8 vs. 37±13 (P<0,05) and CS 64±21 vs. 64±19 (P=NS). Only pts in group A, after therapy, were not found significantly different in PACAP-38 levels, as compared to the CS (P=NS).
Conclusion: Six months antihypertensive monotherapy with the I1-imidazoline agonist moxonidine, the dihydropyridine calcium antagonist amlodipine and the non-dihydropyridine calcium antagonist diltiazem resulted in significant elevation in PACAP-38 plasma levels of HS and in this context may all provide neurotrophic-neuroprotective action.

SOCIAL ASPECTS OF CARDIOVASCULAR DISEASE

P3714 How certain can we be when generalizing from the results of clinical research to routine practice?

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Background: Randomized controlled trials have been the cornerstone of much clinical research, yet they have commonly excluded as many as 90% of patients for whom the intervention might be used in routine practice. Consequently, generalizability is often an issue when using clinical trial results to estimate outcome probabilities in usual care. We sought to assess whether similar limitations might pertain to the relatively larger proportion of patients consenting to passive follow-up in observational population-based studies. Methods: We compared the demographic and clinical characteristics of the 3305 patients (41.1%) consenting (C) to long term observational follow-up in the baseline phase of a population-wide cardiovascular disease management study (Improving Cardiovascular Outcomes in Nova Scotia (ICONS) [Oct 15/97-Oct 14/98]) versus the 4737 who were not consenting (NC). Results: In virtually every instance, marked differences were seen in C vs NC. Examples include mean age (63.7 vs 71.0 years, p<0.00001), gender (35.8% vs 47.5% female, p<0.00001), and history of hyperlipidemia (43.9% vs 23.0%, p=0.0047), diabetes (24.7% vs 26.3%,p=0.1185), hypertension (49.8% vs 47.4%,p=0.0411), and smoking (60.7% vs 48.1%,p<0.00001). Other important differences included prior CHF (10.5% vs. 21.5%), prior MI (35.0% vs. 27.9%), previous stroke (5.4% vs. 8.7%), and previous revascularization (24.5% vs. 12.9%), all of which were significant at a p<0.00001 level. Marked differences in outcome, including 12 month mortality (2.8% for C and 16.3% for NC, p<0.00001), were noted as well. Conclusion: Generalizability is a pervasive problem in clinical research, even when consent rates are high. We suspect that even where "representative sampling" is applied, individual willingness to participate can bias findings. Society will need to balance protection of individual rights to privacy against the need to understand the epidemiology of disease and its treatment if assessments of patient management and outcomes are to progress beyond the limited insights that can be provided by administrative data.

P3715 Losartan reduces the burden of ESRD: public health implications from the RENAAL study for the European Union

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Background: Type 2 diabetes is the leading cause of end-stage renal disease (ESRD) in most industrialized countries in Europe. The RENAAL (Reduction in Endpoints in NIDDM with the AII Antagonist Losartan) Study was a randomized, double-blind, placebo-controlled, multi-national clinical trial of losartan versus placebo on a background of non-ACE/non-AIIA conventional antihypertensive therapy designed to evaluate the renal protective effects of losartan in 1,513 patients with type 2 diabetes and nephropathy. Losartan reduced the incidence of doubling of serum creatinine, ESRD, or death by 16% (p=0.024)and the onset of ESRD defined as the initiation of dialysis or renal transplantation by 28% (p=0.002).
Objective: To extrapolate the potential effect of losartan on the burden associated with ESRD over 3.5 years in the European Union (EU).
Methods: New ESRD cases avoided is calculated by combining type 2 diabetes population estimates for the EU with the percent absolute risk reduction of ESRD (6.1%: 95% CI 1.1 to 10.9; p=0.015) observed in RENAAL over 3.5 years. The number of days each patient experienced ESRD was defined as the length of time from onset of ESRD until the minimum of death or study end. Compared to placebo, losartan reduced the number of days with ESRD by 33.6 (95% CI: 10.9 to 56.3, p=0.004) per patient at risk over 3.5 years. ESRD-free years is calculated by combining the population estimate with the ESRD-free days divided by the number of days in a year (365.25).
Results: EUROSTAT (2000) reports 17.1 million individuals with diabetes in the EU. An estimated 700,000 are diagnosed type 2 diabetics with proteinuria (urine albumin/creatinine >= 300mg/g). Extrapolating the results of RENAAL to these patients we may expect the addition of losartan to the treatment regimen of these patients to lead to a reduction of 42,700 cases of ESRD and 64,400 fewer years with ESRD over 3.5 years.
Conclusion: Treatment with losartan not only reduced the incidence of ESRD, but can also result in a substantial reduction in the burden of ESRD in the European Union.

P3716 Comparison of the Zung self rating depression scale in patients randomised to coronary artery bypass grafting or percutaneous coronary intervention: results from the SoS trial

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Background: Psychological depression has a high prevalence in patients with coronary artery disease and has been reported as an independent predictor of clinical events. We compared symptoms of depression in patients treated with coronary artery bypass grafting (CABG) or percutaneous coronary intervention with stents (PCI).

Methods: In the SoS Trial 988 patients were randomised to CABG or PCI from 53 centres in Europe and Canada. Patients were considered eligible if they were considered suitable by both the surgeon and the interventionist for coronary revascularisation. Depression was assessed with the Zung Self Rating Questionnaire which has 20 items describing depressive symptoms. The questionnaires were translated into the local language and administered at baseline, 6 and 12 months of follow up. The results are presented as a score between 25 to 100. Patients with scores less than 50 are considered not depressed, between 50 to 60 mildly depressed, over 60 moderately depressed and over 70 severely depressed.

Results: Of the 988 patients randomised into the trial 90.8% completed the Zung at baseline and at least one follow up: CABG 456, PCI 441. The mean score at 6 months was 46.0 in the PCI group versus 44.5 in the CABG group, difference 1.4, 95% CI -0.1 to 2.9, p=0.066. At 12 months the score was 45.3 in the PCI group versus 44.6 in the CABG group, mean difference 0.7, 95% CI -0.9 to 2.2, p=0.41. Both groups showed a small decrease in score at 6 months and 12 months compared to baseline (see table 1). Adjusting for age and beta blockers made no difference to results.

Table 1: Zung mean change from baseline

Mean change (SE)	PCI	CABG	Mean difference (95% CI)	p-value
6 months	-1.5 (0.5)	-4.0 (0.5)	2.0 (0.7 to 3.3)	p=0.004
12 months	-2.2 (0.5)	-4.0 (0.5)	1.3 (-0.0 to 2.6)	p=0.054

Mean change from baseline to 6 and 12 months is shown. Mean difference is estimated for the mean in PCI group minus the mean in the CABG group using analysis of covariance adjusted for baseline values

Conclusion: Mean scores suggest that depression is not a major factor of patients enrolled in the SoS trial. Patients in both group have similar Zung index scores at 6 months and 12 months and show improvement from baseline but the change from baseline is greater in the CABG group.

P3717 Relation between clinical features and psychological factors in women with coronary heart disease

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Background: Although psychological factors including anxiety, depression, and somatic concerns have been suggested to be a possible cause and/or a trigger of coronary heart disease in women, the evidence supporting this hypothesis is still controversial. The present study was undertaken to assess the relation of psychological status with clinical symptoms in 92 consecutive women presenting with chest pain and inducible ischemia, as shown by exercise stress testing and reversible myocardial perfusion abnormalities.

Methods: All pts underwent quantitative coronary arteriography and 24-hrs ambulatory ECG recording. 22 pts (Gr1) showed normal or almost normal coronary angiograms (maximal stenosis <20%). The other 70 pts (Gr2) were found to have CAD. Psychological profiling was evaluated by the Beck Depression Inventory, Hamilton Anxiety Rating Scale (HAMA), State-Trait Anxiety Inventory (STAI Y-1 and Y-2) and State-Trait Anger Expression Inventory (STAXI).

Results: The scale measuring emotional involvement (STAXI) showed no significant difference between Gr1 and Gr2. Conversely Gr1 scored significantly higher than Gr2 ($p<0.05$ each) on the remaining tests. 12/22 Gr1 and 4/70 Gr2 pts had a score > 28 in HAMA (Gr1A and Gr2A- frank psychiatric abnormalities). The remaining pts were grouped as Gr1B and Gr2B. No significant differences between Gr1 and Gr2 were found in exercise capacity (time to 0.1 mV ST depression: 397 ± 73 vs 419 ± 137 sec.). In contrast, the number of chest pain episodes per week, as assessed in the last month before admission, was greater ($p<0.01$) in Gr1 than Gr2 (1.9 ± 0.3 vs 0.6 ± 0.4). 24 hrs ECG Holter monitoring showed a significantly higher ($p<0.02$) number of ischemic episodes in Gr1 than in Gr2 (1.6 ± 1.7 vs 0.3 ± 0.3). Significance was greater ($p<0.01$) if comparing Gr1A (2.8 ± 1.3) to Gr1B (0.6 ± 0.2), or Gr2A (1.2 ± 0.8) to Gr2B (0.1 ± 0.4).

Conclusions: (1) A history of anxiety disorders is a common finding among women with chest pain symptoms and normal or almost normal angiograms, but may occur also in CAD. (2) Anxiety correlates with increased transient myocardial ischemia and symptoms during daily life. (3) Potential pathways include the effects of the sympathetic nervous system on coronary circulation. (4) The implication is that treatment and rehabilitation of these women should focus on improving their psychological trait.

P3718 Socioeconomic status and psychosocial factors are related to glycated haemoglobin in non-diabetic men and women

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Background: Glycated haemoglobin (HbA1c) is an indicator of average blood glucose concentration over the previous 2-3 months, and may be a marker of impaired glucose tolerance in non-diabetic populations. Other measures of the impaired glucose tolerance and the metabolic syndrome have previously been associated with low socioeconomic status (SES). This study assessed the relationship between HbA1c and SES, and associations with psychosocial and behavioural factors relevant to cardiovascular disease risk.

Methods: Participants were 234 non-diabetic men and women aged 47-59 who were part of the Whitehall II epidemiological cohort. SES was defined by grade of employment. Psychosocial factors were assessed using standardized questionnaires.

Results: Glycated haemoglobin ranged from 4.43 – 6.49%. There was a significant trend in HbA1c across grades of employment (P =.016), with mean (s.e.m.) levels of 5.30% (.032) in higher status, 5.34% (.034) in intermediate status, and 5.42% (.037) in lower status groups, after adjustment for age and sex. HbA1c concentration was positively associated with waist/hip ratio (P <.004) and negatively related to alcohol consumption (P =.033), but was not associated with body mass index or smoking. People who reported low control at work (P = 0.026), low internal locus of control (P =.003), low use of active coping strategies (P =.011) and low social supports (P <.001) had higher HbA1c levels. After taking age, sex, waist/hip ratio, alcohol and grade of employment into account, an independent association between low social support and elevated HbA1c remained (P <.001).

Conclusions: Glycated hemoglobin is inversely associated with SES in non-diabetic middle-aged men and women. Impaired glucose tolerance is also related to psychosocial factors that have been implicated in cardiovascular disease risk. These findings are consistent with the hypothesis that SES and psychosocial factors increase risk for coronary heart disease partly through disturbances in metabolic function.

P3719 The cost of treating angina pectoris in the United Kingdom

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Aims: The prevalence and cost of treating angina pectoris (AP) remains high in "developed" countries. This unique study evaluated the contemporary cost of AP to the National Health Service (NHS) in the UK during the calendar year 2000.

Methods: We applied contemporary estimates of AP-related health care activity to the whole UK population, on an age and sex-specific basis, to calculate its cost to the NHS. Direct costs included were hospital admissions associated with a principal diagnosis of AP and unstable AP, coronary artery by-pass [CABG) and percutaneous angioplasty PTCA procedures, associated outpatient (OPD) consultations, General Practitioner (GP) consultations and prescribed drug therapy. A number of sensitivity analyses were performed to account for potential variances in baseline estimates and the likey impact of changes in the pattern of treating AP.

Results: We estimate that 634,000 individuals (1.1% of the UK population) were actively treated for AP within the community during 2000. These individuals required a total of 2.35 million (m) GP consultations, 16 m individual prescriptions and 254,000 OPD consultations at a cost of £51 m, £81 m and £30 m, respectively. We also calculated that there were a total of 149,000 hospitalisations related to AP; that 117,000 coronary angiograms, 21,400 CABG and 17,700 PTCA procedures (70% of which included placement of an intracoronary stent) were performed and that there were 516,000 post-discharge OPD visits. The cost of each of these was estimated at £208 m, £70 m, £106 m and £61 m and £52 m, respectively. The total direct cost of health care for these patients was, therefore, calculated to be £659 m or 1.3% of total NHS expenditure. Hospital bed utilisation and in-hospital procedures accounted for 32% and 35% (combined 67%) of this expenditure. Sensitivity analyses showed that revascularisation procedures exert the greatest potential inflationary pressure on the total cost of AP. For example, the cost of treating AP would increase by about 4% (£25 - 27 m more) if: a) the prevalence of AP were 20% greater or b) there was a 10% increase in hospital activity. However, if revascularisation rates in the UK approached those of mainland Europe, the total cost of treating AP would increase by £107 m (a 16% increase overall).

Conclusions: Angina pectoris is a major and costly health problem in the UK. It consumed over 1% of all NHS expenditure in the year 2000 - the predominant cost components being hospital bed utilisation and revascularisation procedures. This is likely to be a conservative estimate of its true cost.

P3720 Quality of life in unstable angina – Individual and public preferences differ in levels but are similar when measuring changes over time

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Background & Aim: There is a need for easily administered quality of life evaluations in the clinical setting. The quality adjusted life year (QALY), incorporating in a single measure length of life and quality of life, is a widely used outcome measure in health economic evaluations. The valuation of the quality component in QALYs has been debated. The quality adjustment should mirror preferences for health states but there are different approaches to whose preferences should be used. To illuminate this question empirically we compared patients' valuations of health states they were actually experiencing with the valuations of the same health states from the general public.

Material & Methods: In the randomised FRISC II clinical trial, 341 patients with unstable coronary artery disease valued their quality of life at the acute phase of the disease (the patients were admitted to hospital due to an episode of unstable angina or non-ST-elevation myocardial infarction) and at follow-up after 3 months. Patients' preferences were measured by interviews, using the time trade off technique (TTO). The patients also completed the EuroQol questionnaire, where preferences for defined health states from the general public are available, also elicited by the TTO technique (known as the social tariff).

Results: Average TTO value at the acute phase of disease was 0,75 compared to 0,71 using social tariff values. At three months, average TTO value was 0,81 and average social tariff value was 0,78, representing a quality gain of 0,06 and 0,07 respectively. Comparing TTO values to social tariff values for defined health states show small differences for "mild" health states but for "severe" health states TTO values are generally higher than social tariff values.

Conclusions: Quality of life associated with unstable coronary artery disease is valued higher by the patients than by the general public. Results indicate that using the social tariff from the easily administered EuroQol could be a useful proxy for individual preferences when measuring average changes in quality of life over time.

P3721 Deciding on cardiopulmonary resuscitation (CPR) and the European Convention on Human Rights: experience in a Scottish teaching hospital

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Introduction At its introduction in the 1960s the decision on whether to initiate cardiopulmonary resuscitation (CPR) on hospital patients was seen as a clinical one. Recent European legislation and national policy documents have emphasized the importance of patients' wishes and patients' rights. Shortly before these came into effect we carried out a study of deaths in a Scottish acute teaching hospital, finding what was recorded in the notes, comparing these with the parallel records produced by the hospital resuscitation team. The results are relevant to the practicalities of attempting to conform to human rights legislation. **Methods** Records of hospital deaths occurring during six months of 1999 were requested for all patients of age 15 and over. The record of the fatal admission was studied for what was recorded on decisions, discussions and actions on cardiopulmonary resuscitation. CPR records produced by the on-call team were collected and examined over the same period.

Results The study was difficult and laborious. Access to case records was delayed up to one year. CPR records had to be chased and secured. What was recorded in the notes was often insufficiently precise for our purposes. During the six month period there were 574 deaths. In 72% of these death was anticipated and in 63% a resuscitation policy was recorded. Discussion with relatives was recorded in 39% but their existence or availability was not routinely recorded in the others. A written record of discussion with the patient was found in 3% of records. Attempted resuscitation was recorded in 99 cases (17%), by definition unsuccessful. Over the same period 120 CPR records were obtained with 19 false alarms and an initial success rate of 44%.

Conclusion Monitoring or audit of resuscitation policy as health departments now require proved to be too laborious done in this way to be routine. Most deaths in this acute hospital were expected and in many of these cases anticipatory discussions had been held with relatives and recorded. This was not true of the patients themselves. Only 17% of deaths were the subject of CPR. There is therefore a chasm to be bridged between previous practice and the apparent demands of legislation and human rights activists. Paradoxically, moribund patients are least able to give informed consent to the withholding of CPR, while fit patients, able to discuss the issue, are most unlikely to suffer cardiac arrest or have CPR withheld. Means of bridging the chasm and resolving the paradox will be discussed.

P3722 The appropriateness of prescription of non-invasive diagnostic tests in cardiology

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To tackle the problem of the waiting lists of non-invasive diagnostic tests in cardiology, we evaluated the appropriateness of prescriptions of echocardiography, exercise test, Holter monitoring and vascular sonography performed during 4 weeks in ambulatory patients in Tuscany, Italy. Methods: before performing the exam, the appropriateness of the prescription (according to Italian guidelines; class I appropriate, class II doubtfully appropriate, class III inappropriate) and the prescribing physician (general practitioner [GP] vs cardiologist) were recorded. After having performed the exam, the diagnosis (normal vs abnormal) and the clinical utility (useful [if the exam influence the clinical decision-making process] vs unuseful) were registered. Results: we evaluated 5614 records (mean age of patients 63 years, range 14-96; 2587 females) of which 2719 were prescriptions of echocardiography, 1158 of exercise testing, 863 of Holter monitoring and 874 of vascular sonography. Prescriptions were of class I in 45.3% of the cases, of class II in 34.8% of the cases and of class III in 19.9% of the cases. The test was abnormal in 43.8% of the cases; in particular, it was abnormal in 58.3% of class I, in 40.4% of class II and in 17% of class III prescriptions ($p<0.05$). The test was useful in 51.2% of the cases; in particular, it was useful in 72.4% of class I, in 43% of class II and in 17.1% of class III prescriptions ($p<0.05$). A decrease in the incidence of abnormal exams was detected moving from class I to class II and to class III exams (OR 0.40, 95% CI 0.37 to 0.44; $p<0.05$). Similarly, a decrease in the incidence of useful exams was detected moving from class I to class II and to class III exams (OR 0.28, 95% CI 0.26 to 0.30; $p<0.05$). Prescriptions were made by cardiologists in 1882 cases (33.5%); their prescriptions were of class I in 57.3% of the cases, of class II in 32.4% of the cases, of class III in 10.3% of the cases vs 39.2%, 36.1% and 24.7% of GPs' prescriptions ($p<0.05$). Cardiologist-prescribed exams were abnormal in 53.4% of the cases vs 39% of GP-prescribed exams (OR 1.76 95% CI 1.58 to 1.97; $p<0.05$). Cardiologist-prescribed exams were useful in 64.7% of the cases vs 44.4% of GP-prescribed exams (OR 2.26, 95% CI 2.02 to 2.53; $p<0.05$). Conclusions: 1) In Tuscany, Italy, more than half of the prescriptions for non-invasive cardiological tests are inappropriate. 2) Appropriately-prescribed exams give a higher rate of abnormal and useful results. 3) Cardiologists-prescribed exams are more often appropriate, abnormal and useful in respect to GP-prescribed exams.

P3723 Psycho-social factors of cardiovascular disease death risk during the period of reforms in Russia

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Since 1992 an evident growth of cardio-vascular disease mortality rate has been registered in the Russian Federation (RF). That period coincided with socio-economic reforms held, which had drastically changed the life of the most of RF population. In Kabardino-Balkarian Republic (KBR), one of the RF Southern Regions, a high mortality rate in the able men represents one of the most pressing problems. The main causes of death are accidents and cardio-vascular diseases (CVD).

The aim of this research is to study the prognostic relationships between the dynamics of a number of economic and socio-psychological parameters, and that one of CVD-caused mortality. Using the Programme methods, recommended by The State Centre for Prophylactic Medicine, quality and mode of life of 1,340 men, aged 35 to 60, have been studied in the Town of Nalchik and rural areas, including their attititude to reforms. In addition, the RF/KBR (State Committee for Statistics) Goskomstat-provided data on the basic socio-economic parameters of the KBR population's life has been analyzed. Multiple regression analysis has been carried out.

Results obtained: Strong correlations between the CVD-caused mortality rate and dynamics of murders (R=0.63), suicides (R=0.71) have been established. Murders and suicides indirectly characterize a condition of aggressivity and despair in the community. In 70% interrogated an attitude to reforms proved to be negative, with incomes of 40%. lower than minimum life standard; 15% rural-areas inhabitants and 20% town-dwellers having no permanent jobs. CVD-caused mortality rate has been actually influenced by nutrition (R=0.47). Within the recent decade, a consumption of meat by the KBR population has been decreased by 28%, vegetables – 18%, fruits – 34%, with the bread consumption increased by 23%. As known, alterations to the structure of nutrition due to the bread consumption growth on the background of lower consumption of expensive foods, indicates to population's life standards degradation.

Conclusions: Results obtained show, that the CVD-caused mortality rate growth in KBR within the recent decade, has been promoted by the increasing stress level, deterioration of living conditions and negative nutrition structure changes, in relation with reforms held.

P3724 Comparative costs of chest pain unit versus coronary care unit management of acute coronary syndromes without ST-segment elevation

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Background: Acute coronary syndromes without ST elevation (unstable angina, UA; non ST elevation myocardial infarction, NSTEMI) represent a common cause of hospital admission and involve very high costs. Chest pain unit (CPU) management of these patients (pts) may represent a cost-effective alternative to coronary care unit (CCU) admission. Patients and Methods. During 2001, 142 consecutive pts (mean age 71 y, range 44-92, male 66%) with UA or NSTEMI were treated with GP IIb/IIIa antagonist in addition to standard pharmacologic treatment. Patients were randomly assigned to CPU-management (angiography depending on: recurrent angina, troponin > 0.10 ng/l, D ST, EF < 40%) or CCU-management (early invasive strategy encouraged). Patients were followed-up for CE in-hospital and at 6 months. Results. The two subsets of CPU-pts (n=73) and CCU-pts (n=69) shared similar baseline features, troponin levels, TIMI risk score, and presence of UA or NSTEMI on admission. PTCA was performed in 33% CPU-pts versus 49% CCU-pts (P<.05); CABG in 5.5% versus 5.8% (P=ns). Patients with TIMI risk score <4 (n=82) were managed by angiography and PTCA within 24 hours in 7% and 32% respectively in CPU versus 37% and 66% in CCU (P<.01). Length of stay was 2.4 days in CPU-pts versus 3.6 days in CCU (P<.01). Direct discharge rates were similar (13.7% from CPU versus 14.5% from CCU (P=ns). For pts transferred to the wards, average in-hospital stay was 6.9 days (CPU) versus 6.2 days (CCU)(P=ns). The crossover rate from CPU to CCU, due to clinical instability, was 11%. Average cost of diagnostic and treatment strategy, total differential costs and total costs were 1829, 4453 and 5.955 Euro in CPU-pts, versus 2441, 5275 and 7160 Euro in CCU-pts (P=ns; P<.05; P<.05, respectively). The management of pts with TIMI risk score <4 (n=82), had lower average costs in CPU-pts -56%,-11%,-26% as compared to CCU-pts (P<.01,P<.05,P<.5, respectively). Of note, the outcome in terms of CE in-hospital and at 6 months was not different in the two groups (P=ns). Conversely, no difference were found in pts with TIMI score =/>4 (n=60) managed by CPU or CCU. Conclusions. Management in CPU of pts with UA and NSTEMI is a cost-effective alternative to CCU management; involves less frequent use of high-cost invasive procedures; does not increase the likelihood of in-hospital and short-term recurrence of ischemic events.

P3725 Study improving compliance in hypertension and diabetes with the use of a new talking pill reminder: the SIC trial

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Background: Patient compliance (C) is poor in hypertension and diabetes, non-C causing therapeutic failures frequently in all chronic diseases. Traditional interventions to improve C proved to be quite futile in leading to better therapeutic results.

Methods: Hypertensives and type-2 diabetics were enrolled into the study, treated minimally for one year, taking more than two, different drugs per os, minimally twice daily. Blood pressure (BP)self-measurement was perfomed twice daily in pre-set intervals. To improve C a new, pocket-size, talking pill reminder device was used, reminding the patient by the voice of the personal physician of pill intake and/or other regular daily activities like BP measurement. Receiving these messages are indicated by the patient pushing a button, and if this signal is not given, the message is repeated twice in 30-min intervals. Half of the patients were bringing home the device, programmed for their personal medication schedule and took their pills for a month accordingly, than gave back the device, received verbal and written counseling and continued treatment for another month, the other group started treatment with the traditional compliance-improving aids, then changed for the programmed device for the second month. 40 uncontrolled mild-moderate hypertensives and 20 diabetics were enrolled, 39 out of the 60 were females, age 63±12 years, mean BMI 27.4 (females) and 26.3 (men). Results of the two compliance-improving techniques were compared by paired-observation t-test and nonparametric tests.

Results: There was a trend in decreasing both systolic- and diastolic BP with both compliance-improving techniques, but no significant difference between the two periods. There was, however, significantly lower blood-sugar values ($p<0.05$) during the period when the talking reminder was used. The device was preferred by 92% of patients, and by all physicians as compared to the traditional verbal counseling and written reminder.

Conclusion: Mobile, pocket-size talking pill reminder device might significantly improve patient compliance in subsets of patients with poor adherence to therapy. For more detailed data in this field, more controlled studies are needed.

P3726 Are patients really taking aspirin 6 months after an acute myocardial infarction?

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Nonadherence to (noncompliance with) medical treatment following an acute myocardial infarction (MI) may increase the risk for recurrent adverse events. Therefore, we investigated adherence to Aspirin treatment in a cohort of outpatients after acute MI.

Patients and Methods: To determine which objective adherence detection method should be used, we first studied platelet-aggregation indices (TxB2 production and platelet aggregation induced by different concentrations of Collagen) in a small group of subjects whose Aspirin intake was known. Based on these values, we have divided aggregation results into three groups: adherent, partially adherent and nonadherent. For the "field" study, 100 consecutive patients were scheduled for a routine clinic visit 6-months after an acute MI. All patients were asked not to take their usual morning medications prior to the visit. Consent was obtained upon arrival to the clinic, Aspirin dose was ascertained by questioning, and patients who said that their prescribed Aspirin dose was 100 mg daily were asked to give a blood sample and answer an adherence self-report questionnaire.

Results: Of the 100 patients who were called, 82 came to the clinic.. Eleven reported that they had been prescribed a different dose of Aspirin and six refused to give informed consent. "Full adherence" to Aspirin treatment was determined to be 51% by TXB2 production (the preferred method according to the preliminary analyses). Partial adherence was seen in 21% of the subjects and nonadherence was found in 27%. The results of the adherence questioner where not related to actual adherence.

Conclusions: These results suggest that in "real life" adherence to medical treatment is lower than reported in controlled medication trials that. This may adversely affect patient's outcome and therefore objective adherence monitoring should probably be incorporated into standard practice.

P3727 Afternoon nap significantly affects the circadian periodicity for the time of onset of acute myocardial infarction

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Previous studies have indicated that a circadian periodicity exists for the time of onset of acute myocardial infarction (AMI), with a morning peak incidence of events. This circadian variation has been attributed to rises in plasma catecholamines and cortisol and increases in platelet aggregability prior to awakening, and is lost with treatment with beta-blockers or aspirin. However, it is not known whether afternoon nap, common in southern European populations, affects this circadian variation.

Methods: We examined the medical records of all patients admitted with AMI between January and December 2001. The time of onset of chest pain was recorded. Patients accustomed to an afternoon nap (>5 days/week, for >1 hour), (group A), were compared to patients who never rested in the afternoon during the preceding 5 years, (group B). Patients receiving beta-blockers or aspirin were excluded, as were patients who could not be fitted to either group. Circadian periodicity was assessed separately for the two groups, using goodness-of-fit chi-square.

Results: The records of 161 consecutive patients were studied and 95 patients (76 male, mean age 57±13 years) met the inclusion criteria. 56 patients were classified to group A and 39 to group B. Group A displayed a significant (X^2=10.7 $p<0.05$) circadian variability. The incidence of AMI in group A had two peaks, a morning and a marked evening peak. No significant (X2=4.22, $p>0.1$) circadian variability was found in group B.

Circardian periodicity in the two groups

	00 to 06 h	06 to 12 h	12 to 14 h	14 to 20 h	20 to 24 h	total # of pts
nap	9	14	3	24	6	56
no nap	8	10	4	14	3	39

Conclusion: In patients accustomed to afternoon naps, the circadian periodicity for the time of onset of acute myocardial infarction is significantly affected, with most events occurring between 14:00 and 20:00 hours.

P3728 Cognitive function predicts sick leave and early retirement in an unselected population of patients with coronary artery disease

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Aim: To assess the relation between different principal components of health related quality of life (HRQL) and capacity for work in an unselected population of patients with coronary artery disease (CAD)

Design: Cross sectional study.

Setting: Department of Medicine, Södertälje Hospital, Stockholm County Council, Sweden.

Subjects: 171 consecutive pts <65yrs with CAD.

Methods: Health related quality of life was estimated by the generic single item instrument EuroQol (EQ) and the disease specific Cardiac Health Profile (CHP) questionnaire (16 items). Existence and degree of current angina pectoris were ranked according to the Canadian Cardiovascular Society (CCS; 0-4) classification. Reduced capacity for work was defined as sick leave >50% or early retirement >50% (regardless of reason). Multivariate principal components analysis of the CHP-items identified four independent orthogonal domains representing cognitive, physical/general health, social and emotional function.

Results: Patients with reduced capacity for work had a significantly poorer HRQL as assessed by total CHP score respectively EuroQol as compared to those in full work ($p<0.00008$;ANOVA). However, there was no significant difference in relation to CCS class.

Logistic regression showed that both the principal components general health/physical function (p=0.0033) and cognitive function (p=0.0057) of HRQL predicted reduced capacity for work as manifested by early retirement or sick leave. There was no significant dependence between capacity for work and the principal components representing emotional and social function.

Conclusion: We have shown that perceived cognitive function is an independent predictor of sick leave and early retirement in an unselected population of patients with coronary artery disease.

P3729 Enzymatic infarct size (LDHQ48) as endpoint in randomized trials in non-ST-segment elevation acute coronary syndromes undergoing early coronary angiography

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Background: It is suggested that enzyme rise in patients with acute non-ST elevation acute coronary syndromes (ACS) is due to microembolization of thrombotic material from a ruptured plaque and that immediate coronary intervention of this 'hot' plaque may increase distal embolization. By merely taking the incidence of recurrent myocardial infarction as an end point, one may miss early re-infarctions or infarct-extension in pts whose enzymes have not returned to normal values. The assessment of enzymatic infarct size (LDHQ48) takes total enzyme release over a period of time into account and may better quantify the effect of pharmacological or mechanical intervention. **Patients and Methods:** From April 2000 to Dec 2001, 220 pts with unstable angina, Braunwald class 3, with >1 mm ST depression or a positive trop T (>0.05 ng/ml) were randomised to very early (<12 hrs) angiography (group A) without 2b/3a treatment or to angiography after 24-48 hrs pre-treatment with tirofiban (Group B, 0.4 μg/kg/30 min,/0.1 μg/kg/min 24 hrs). Enzymatic infarct size (LDHQ42) was assessed by the area under the LDH release curve from at least 5 measurements over a period of 48 hrs. All angiography films of patients were analysed by an independent core-lab. **Results:** 75% of patients had elevated trop T on admission or 3 hrs thereafter. Median time to angiography was 6 (grp A) and 51 hours (grp B). During initial hospitalization, revascularization was performed in 75% (PTCA: 61%, CABG:14%, grp A) and 77% (PTCA: 58%, CABG: 19%, grp B) of patients.

	Group A (N=109)	Group B (N=111)	P-value
CPKmb positive	53 (49)	57 (51)	0.69
CPKmb max (SD)	92 (91)	79 (68)	0.43
LDHQ48 (SD)	407 (471)	242 (353)	0.004
negative troponin T(N=50)	278 (499)	191 (260)	0.88
positive troponin T (N=152)	412 (441)	257 (369)	0.004

Conclusion: This study shows that in high risk non ST elevation ACS pts, the use of enzymatic infarct size as an end point is feasible and may overcome the issue of different definitions of myocardial infarction. It may better quantify the effect of mechanical or pharmacological intervention on total enzyme release, compared to a clinical end point alone.

P3730 Composite endpoints in trials after myocardial infarction: lessons from CAPRICORN

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Background: CAPRICORN, a randomised double blind placebo controlled trial in patients with acute myocardial infarction and left ventricular dysfunction, demonstrated a 23% mortality reduction (p=0.031), and significant reductions for major coronary events. Despite significant trends in individual components of CV hospitalisations, the co-primary endpoint of all-cause mortality or CV hospitalisation showed only a positive trend for carvedilol (p= 0.30). The abstract explains this apparently paradoxical result. **Methods:** For four mutually exclusive categories: all death, non-fatal myocardial infarction, heart failure hospitalisation "all other CV" hospitalisations, the numbers of cause specific events and of first events in the composite endpoint, and the numbers of 'hidden' events behind lead non-fatal events were identified. **Results:** The table below gives the cause specific and the lead events in the co-primary endpoint. Many deaths prevented by carvedilol lie behind earlier non-fatal events. Benefits in reducing non-fatal MIs lie behind heart failure or "all other CV" events, and heart failure benefits lie behind "all other CV" events. **Conclusion:** In the "time to first event" analysis of the composite endpoint, the benefits of carvedilol were masked by earlier non-fatal events. Therefore care must be exercised in the adoption of general composite endpoints in trials of myocardial infarction particularly if there is likely to be a high incidence of minor and/or early events which may not be susceptible to reduction by the treatment tested.

Abstract P3730 – Table

Event Category	Placebo (n=984) category specific number	Placebo (n=984) composite first event numbers	Carvedilol (n=975) category specific number	Carvedilol (n=975) composite first event numbers
Death	151	83	116	66
Non Fatal MI	57	45	34	27
Heart Failure	138	101	118	97
All Other CV	194	138	189	150

TRANSCORONARY ABLATION IN HYPERTROPHIC CARDIOMYOPATHY

P3731 Role of transcoronary ablation of septal hypertrophy (TASH) for HCM and mild outflow obstruction even under provocable conditions

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To evaluate the role of catheter interventional treatment in pts. with HCM and only mild outflow obstruction even under provocable conditions, the symptomatic and haemodynamic benefits of transcoronary ablation of septal hypertrophy (TASH) were compared in 22 pts. with a mild provocable gradient <=50 mmHg (range 10-50 mmHg, 32±15 mmHg, Group I) and in 252 pts. with a marked provocable gradient >50 mmHg (range 55-300 mmHg, 150±45 mmHg, Group II) At baseline Group I pts. had a significantly lower gradient at rest (12±8 v. 56±42 mmHg, p<0.001) and after provocation by a single premature ventricular beat (32±15 mmHg v. 150±45 mmHg, p<0.001). However, both groups did not differ significantly with respect to age (58±16 v. 57±15 y), male sex (41 v. 49%), NYHA-FC (2.8±0.6 v. 2.9±0.6), septal thickness (22±3 v. 22±4 mm), exercise capacity (70±36 v. 75±37 watts), peak oxygen consumption (13.6±5.3 v. 15.1±5.7 ml/kg/min), cardiac index at peak exercise (5.4±2.0 v. 5.7±1.7 l/m^2/min) and pulmonary artery mean pressure at workload (40±12 v. 41±9 mmHg). Seven months after TASH both groups demonstrated a decrease in septal thickness (-35±23 v. -42±19%) and an improvement in NYHA-FC (-1.1±0.6 v. -1.3±0.7), exercise capacity (+24±43 v. +25±37%), peak oxygen consumption (+16±45 v. +13±36%), cardiac index at peak exercise (+24±53 v. +12±36%) and pulmonary artery mean pressure at workload (-13±19 v. -15±19%), that did not differ significantly between pts. with mild and marked outflow obstruction under provocable conditions. However, pts. with only mild outflow obstruction under provocable conditions could be treated by a lower peak CK-activity induced (312±140 v. 515±321 U/L, p< 0.001), a lower amount of ethanol injected (2.0±0.8 v. 2.8±1.8 ml, p< 0.004) and a trend to a lower proportion of re-interventions performed (0 v. 8.7%).

Conclusion: A pronounced symptomatic and haemodynamic improvement after TASH is not restricted to pts. with marked outflow gradients. Similar benefits were found in pts. with no more than mild outflow obstruction even under provocable conditions. Therefore, a marked outflow gradient at rest or after provocation should not be considered a necessary criterion for interventional therapy in pts. with severe symptoms unresponsive to medical treatment.

P3732 Quantification of myocardial injury after percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy

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Background: Percutaneous transluminal septal myocardial ablation (PTSMA) is a nonsurgical therapeutic procedure for reducing left ventricular outflow tract obstruction in symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM). The aim of this study was to evaluate septal myocardial injury size after PTSMA using delayed contrast-enhanced (DCE) magnetic resonance imaging (MRI).

Methods: 16 patients (mean age 50±16 years, 8 males) underwent MRI before and 4 weeks after PTSMA; volume of ethanol injected during procedure was 1 to 5 mL. Images were acquired on a 1.5 T scanner (Vision/Sonata, Siemens, Erlangen, Germany). Cine gradient-echo MRI was performed for assessment of global left ventricular function at baseline and follow-up. Inversion-recovery turbo-FLASH images (TE 3.4 ms, TR 7.6 ms, TI 250-300 ms) were acquired at follow-up, 20 to 30 minutes after i.v. administration of 0.2 mmol/kg gadolinium-DTPA. Left ventricular function parameters, myocardial mass, and hyperenhanced area's (including central dark zones of hypoenhancement) were quantified using the MASS software package (Leiden University Medical Center, the Netherlands).

Results: Left ventricular mass values before and after PTSMA were 233.5 ± 68.1 g vs. 220.2 ± 67.6 g (p<0.001), respectively. Septal myocardial mass pre- and post PTSMA was 80.4 ± 26.8 g vs. 72.1 ± 24.0 (p<0.001), resp. In all patients the injured myocardium was well visualized. The hyperenhanced septal myocardial mass ranged from 3.1 to 33.5 g [mean: 14.6 ± 9.2 g], involving 6.8% ± 4.4 of the post-ablational total LV mass and 21.0% ± 14.0 of the septal myocardial mass. Myocardial injury size was not correlated with the volume of ethanol administered.

Conclusions: The extent of myocardial injury after PTSMA can be determined using DCE-MRI and was not correlated with the volume of ethanol administered. The method may serve as control and feedback for the interventional procedure.

P3733 Left ventricular remodelling following the induced septal infarction in obstructive hypertrophic cardiomyopathy

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Non-surgical myocardial reduction (NSMR) is a novel method of non-pharmacological therapy for obstructive hypertrophic cardiomyopathy (HOCM). NSMR results in reduction of the left ventricular outflow tract (LVOT) gradient with symptomatic improvement in patients (pts) with HOCM. However, long-term consequences of induced septal infarction (SI) has not been thoroughly studied.

Methods: In 45 consecutive pts (25 M), followed mean 39.5±4.9 months after NSMR, 2-D and Doppler echo were done at baseline (B), at discharge, and at 3,6,12,24,36 month (mo) follow-up (FU). Echocardiographic measurements (EM) of left ventricle (LV) assessed in this study included: LV end-diastolic dimension (LVDD), LV end-systolic dimension (LVSD), septal thickness (IVS), LV posterior wall thickness (PW), LV ejection fraction (LVEF), LVOT gradient (LVOTG) and mitral regurgitation (MR). We compared results of EM at 36 mo FU to B, and to short-term results (3 mo FU) and to results at 24 mo FU.

Results: 1. The comparison of the EM values at 36 mo FU to B showed following changes: both LVDD and LVSD (43.6±18.4 vs 48.1±5.4mm, p=.0001, and 23.6±4.3 vs 31.6±7.9mm, p=.0001 respectively) increased; IVS (20.8±4.8 vs 16.3±3.6 mm, p=.0001) decreased and PW showed trend to decrease (13.1±3.3 vs 12.4±2.2 mm, NS); LVEF (75.4±9.1 vs 64.5±11.2%, p=.0003) decreased; LVOT gradient was reduced (81.8±26.1 vs 25.4±22.7 mmHg, p=.0001), MR also decreased (2.6±0.5 vs 1.4±0.7,p=.0001). 2. The comparison of the results at 36 mo FU to those at 3 mo FU showed further reduction of LVOT gradient (35.9±28.1 vs 25.4±22.7mmHg, p=.01) and further increase of LVDD and LVSD (45.0±5.5 vs 48.1±5.4 mm, p=.01 and 25.5±5.2 vs 31.6±7.9 mm, p=.01, respectively) but, LVEF did not differ as compared to short-term FU; IVS decreased (17.8±5.9 vs 16.3±3.6mm, p=.001); MR did not change. 3. The comparison the EM results at 36 mo FU to those at 24 mo FU showed ongoing increase of LVDD (46.6±5.8 vs 48.1±5.4mm, p=.02), but its value was still normal; further decrease of IVS (17.8±5.9 vs 16.3±3.6 mm, p=.05) was also observed. The other EM values did not change.

Conclusion: 1. NSMR results in the LV remodelling which causes some positive results as a substantial decrease of both IVS thickness and LVOT gradient. 2. To assess the risk of LV dilatation further careful evaluations of EM are needed, because of ongoing increase of LVDD and slightly decreased LVEF observed at 3 year FU.

P3734 Long-term outcome after percutaneous septal ablation for hypertrophic obstructive cardiomyopathy

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Introduction: Septal ablation (PTSMA) improves outflow gradients (LVOTG) and symptoms during mid-term follow-up in symptomatic patients (pts.) with hypertrophic obstructive cardiomyopathy (HOCM). We analyzed the long-term outcome (41±11 [24-67] months) of 178 consecutive pts. treated between 1/1996 and 12/1998.

Results: 3 pts. died during in-hospital stay (VF, pulmonary embolism, and pericardial tamponade in 1 pt. each). Mean CK rise was 599±300 U/l. A DDD-pacemaker (DDD-PM) had to be implanted in 13 pts. (7%), 11 pts. (6%) underwent re-PTSMA and 3 pts (2%) myectomy. 4 pts. were lost to follow-up. There were 2 further DDD-PM implantations and 2 ICD implantations (after out-of-hospital CPR for unknown reasons in a 23 year-old woman, and after sustained VT in a 74 year-old man with coexistent coronary artery disease). 7 pts. died during follow-up: due to stroke (88 and 86 years), coexistent obstructive pulmonary disease (76 years), colon cancer (79 years), after unsuccessful out-of-hospital CPR (25 years), and due to unknown causes (76 and 54 years, resp.). Further clinical and echocardiographic data are shown in the table.

	baseline	last follow-up	p-value
NYHA class	2.8±0.6	1.6±0.7	<0.0001
LA diameter (mm)	48±8	45±8	<0.01
LVOTG at rest (mmHg)	60±35	7±14	<0.0001
LVOTG at Valsalva (mmHg)	127±50	20±28	<0.0001
Maximum workload (Watts)	87±53	121±42	<0.0001

Conclusions: PTSMA results in a persistent LVOTG reduction and exercise improvement during long-term follow up. Degeneration of the AV conduction system together with the PTSMA-induced damage may requiere a DDD-PM implantation in individual patients. A total mortality rate of 10/178 (6%) including all procedure-related deaths compares favourably with the reported natural course of this pt. group with severe HOCM.

P3735 Prediction of the risk of pacemaker dependency after septal ablation for hypertrophic obstructive cardiomyopathy

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Background and introduction: Damage of the AV conduction system is a major complication of percutaneous septal ablation (PTSMA) that needs early and reliable identification of patients (pts.) at risk for complete heart block (CHB).
Methods and results: In the first 33 pts. who had PTSMA, 7 required a DDD pacemaker (PM) implantation (PM-rate: 21%). AV conduction recovery needed 11 days in one pt.; another pt. suffered from unexpected CHB 9 days after PTSMA. The 7 PM-pts. of this series were compared to those without conduction disturbances. A score was calculated to identify all PM-pts. retrospectively with >12 points. In the following 265 consecutive pts., this score was applied prospectively. 13 of 14 pts. (93%) who needed a PM (PM-rate: 5%) were correctly identified by the scoring system, while 1 pt. with a score of 13 had conduction recovery after short-term steroid therapy. All pts. with <8 points (n=230; 79%) remained free from conduction disturbance and were discharged from monitoring after 3±2 days (vs. 7±4 days in the pts. with >8 points; p<0.01)

	cutoff value	score points
Baseline PQ interval (ms)	> 160	+ 2
Baseline minimal HR (Holter, bpm)	< 50	+ 2
Baseline gradient (Echo, mmHg)	> 70	+ 2
CHB during PTSMA at any time	yes	+ 2
CHB on arrival at coronary care unit	yes	+ 2
AV conduction recovery after 12 hs	yes	- 2
No AV conduction after 12/24/48 hs	yes	+1 / +2 / +3
QRS duration after 48 hs (ms)	> 155	+ 3
Timing of the GOT peak (hs)	> 16	+ 1
	> 20	+ 3

Conclusions: Based on careful monitoring for the first 48 hours after PTSMA, pts. at risk for CHB can be correctly identified. Pts. with a score <8 are at low, those with >12 points at high risk. In the remaining cases watchful waiting may allow AV conduction to recover, thus reducing the number of PM implantations after PTSMA to a rate of 5%.

P3736 Prognosis of patients with hypertrophic obstructive cardiomyopathy after transcoronary ablation of septal hypertrophy (TASH)

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Background and Methods: TASH constitutes a new catheter based therapeutic option for symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM). Regarding the prognosis after TASH only few data are available in the literature. Based on a validated quality of life questionnaire (QoL) and serial control examinations we analysed the clinical course of all patients treated in our institution up to December 2001.
Results: Between October 1995 and December 2001, 329 pts were treated by TASH (pressure/angiography guided technique, age 60.0 ± 13.1 years, male/female (155/174 pts), 98.8% follow up (325/329 pts), mean follow up time 2.1 ± 1.6 years, maximum 6.2 years). The TASH related total in hospital mortality amounts to 1.8% (6/329pts) and to 0.3% (1/329) excluding 5 pts with severe comorbidity. Sudden out of hospital death occurred in 4 pts and not sudden, not TASH related death in 19 pts (e.g. carcinoma, pneumonia, purulent peritonitis and suicide). Using Kaplan-Mayer life table calculations the corresponding total annual mortality amounted to 4.3% per year. The total cardiac mortality was 1.5% per year including pts with sudden death and 0.6% per year after hospital discharge. The annual cardiac mortality was significant smaller and the QoL-benefit rate of improved pts even somewhat higher (77.3% vs 71.4%, n.s.) in pts treated with small amounts of ethanol (<=2.0 ml vs >2.0 ml ethanol, p=0.031). This amount was an independent prognostic predictor (p=0.047, Cox regression analysis). Advanced age (>61 years) was otherwise a significant predictor of increased prognostic risk in this pt cohort (p=0.002). Regarding the learning curve no significant difference of prognosis was found in two large series of pts (subset pt No 1-165 and 166-329).
Conclusion: There is a low hospital mortality risk of TASH. Prognosis appears to be good. It compares favourable with the prognosis after surgery for HOCM and seems to be significantly better in pts treated with small amounts of ethanol. Apparently there is no difference regarding the clinical benefit from TASH in subsets treated with small or high amounts.

P3737 Role of transcoronary ablation of septal hypertrophy for HOCM, NYHA-FC II and severe symptoms like fatigue, chest pain, palpitations or syncope

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To evaluate the role of catheter interventional treatment in pts. with HOCM and severe symptoms like fatigue, chest pain, palpitations or syncope, we compared the results of transcoronary ablation of septal hypertrophy (TASH) in 51 pts. (Group I) complaining on substantial limitations during daily activity despite dyspnoea did not exceed NYHA-FC II and in 202 pts. (Group II) with NYHA-FC III (174 pts.) or IV (28 pts.).
At baseline Group I pts. were characterized by younger age (48±14 v. 59±15 y.*), a male preponderance (82 v. 40%*), a lower proportion of severe SAM (51 v. 71%*), a lower resting gradient (38±32 v. 57±44 mmHg*), a lower pulmonary artery mean pressure at workload (37±9 v. 42±9 mmHg*) and a higher exercise capacity (116±27 v. 65±31 watts*), max. oxygen consumption (20.3±4.8 v. 13.6±4.8 ml/kg/min*) and cardiac index at peak exercise (7.1±1.1 v. 5.5±1.7 l/m^2/min*). However, postextrasystolic gradient (130±47 v. 144±55 mmHg), LVEDP (19±6 v. 20±6 mmHg), septal thickness (22±3 v. 22±3 mm) and the proportion of familiar HOCM (25 v. 21%) and prior syncope (25 v. 29%) did not differ significantly between groups.
At 7 months after TASH the improvement in outflow gradient (-48±31 v. -56±68% at rest*, -49±40 v. -63±33% after provocation*), septal thickness (-32±20 v. -44±18%*), NYHA-FC (-0.7±0.4 v. -1.4±0.6*) exercise capacity (+7±20 v. +30±38%*) and pulmonary artery mean pressure at workload (-5±18 v. -18±18%*) was significantly more pronounced in Group II. However, both groups were not significantly different with respect to a reduction in severe SAM (-86±36 v. -92±27%) and the reported overall subjective improvement (93 v. 94% of pts.). Furthermore, both groups demonstrated a similar and significant reduction in syncope (-80 v. -90% of pts.). Group I pts. could be treated with fewer complications (2 v. 6%) and permanent total AV-Block (0 v. 13%*), since treatment efficacy was achieved by a significantly lower amount of ethanol injected (2.3±1.0 v. 2.9±1.9 ml*). *p<0.05
Conclusion: The clinical improvement observed, justifies a catheter interventional treatment also in pts. with substantial limitations during daily activity despite their dyspnoea at exertion did not exceed NYHA-FC II.

P3738 Septal ablation for hypertrophic obstructive cardiomyopathy in patients with NYHA Class IV Symptoms

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Background and Introduction: In patients (pts.) with hypertrophic obstructive cardiomyopathy (HOCM) presenting with NYHA class IV symptoms, surgical myectomy has been reported to carry a high perioperative risk. We therefore analyzed our database of 322 consecutive pts. for cases who presented with class IV symptoms at the time of percutaneous septal ablation (PTSMA).
Results: In 16 pts. (5%) PTSMA was performed in a class IV situation. One pt. had previous pacemaker implantation, another one surgical myectomy. Mean age was 71±12 (43-88) years. Medical treatment consisted of Ca^{2+}-antagonists in 12, beta-blockers in 4 pts.. The mean ethanol dose was 3.7±2.2 ml, resulting in a CK peak of 623±360 U/l. During in-hospital stay of 16±5 (8-26) days, one pt. (6%) died, 2 pts. (12%) required DDD pacing, and 3 pts. had successful CPR due to tachy- (n=2) or bradyarrhythmic (n=1) events. During late follow-up, 3 pts. died (88 years: unknown cause after 3 months; 83 years: stroke after 8 months; 79 years: colon cancer after 28 months). From the 12 pts. who had their last follow-up 38±11 (26-65) months post-PTSMA, 3 were in class III, 6 in class II and 3 in class I. Additional results are shown in the table.

Table 1

	baseline	last follow-up	p-value
Left atrial diameter (mm)	52±8	47±5	<0.01
Resting LVOT gradient (mmHg)	94±33	0	<0.001
Provoked gradient (mmHg)	149±58	5±11	<0.001
Maximum workload (Watts)	14±26	66±22	<0.01

Conclusions: In a dedicated clinical setting PTSMA is feasible also in pts. presenting with NYHA class IV symptoms. It results in persistent LVOT gradient reduction and symptomatic improvement during long-term follow up. A total mortality rate of 4/16 (25%) including both procedure-related and non-cardiac deaths in 3 years compares favourably to reported natural history data and to surgical results in these elderly pts. with advanced disease.

P3739 Complete relief of syncope during follow-up in patients with HOCM after successful catheter interventional treatment

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Background: Syncope is common in HOCM and is associated with an increased risk of sudden death. Surgical or catheterinterventional relief of outflow tract obstruction (LVOTG) often leads to a reduction of syncopal events, but the precise mechanism contributing to this beneficial outcome remains controversial.
Patients and Methods: Therefore, we investigated hemodynamic response to exercise, tilt test and baroreflex sensitivity in a prospective manner before and 6.4 ±1.3 months after Transcoronary Ablation of Septal Hypertrophy (TASH) in 18 consecutive symptomatic pts. (5 female, 54 ±14y, range 29-73) with unexplained recurrent syncope.
Results: In all patients a significant reduction of LVOTG, decrease of IVS thickness and improvement in NYHA functional class could be reached by TASH. Within the 6 month follow-up no patient had experienced any episodes of syncope or presyncope. During symptom limited upright and supine bicycle exercise no patient had an abnormal blood pressure response (ABR), neither before nor after effective TASH. Early and late heart rate recovery (1.min/15.min.) after exercise cessation was significantly diminished after TASH (deltaHR 1.min./15.min: -19.7 ±9.6%/-36.2 ±7.9% before vs. -13.8 ±6.3%/-30.1 ±8.6% after TASH, p=0.015/0.025). Head-up Tilt Test (TT) before TASH induced reflex hypotension with syncope in 6 patients. Tilting induced, maximal increase in HR (deltaHRmax) was significantly higher in these 6 patients compared with the 12 patients with negative TT (+29.3 ±17.8% vs. +11.4 ±8.5%, p=0.035). After TASH TT was negative in all patients, whereas in the 6 patient with positive TT before TASH deltaHRmax was diminished significantly from +29.3 ±17.8% before to +13.4 ±12.4% after TASH (p=0.025). Baroreflex sensitivity did not change during follow-up after TASH (11.5 ±8.0 before vs. 11.2 ±6.8 ms/mmHg after TASH, n.s).
Conclusions: 1) In HOCM patients with recurrent syncope TASH leads to complete relief of syncope during follow up. 2) These patients show neurally mediated syncope during tilt testing in 33%, which completely disappears after TASH. 3) There is a significant reduction of exaggerated tilting induced heart rate increase after TASH. This reduction may reflect TASH induced improvement of abnormal vasodilator reflex response 4) ABR at exercise is not a common feature in these patients. 5) Furthermore after exercise cessation there is a significantly diminished heart rate fall during recovery period after TASH. It can be interpreted as a TASH induced normalisation of prior inadequate adaptation of systemic vascular resistance.

MITRAL VALVE DISEASE

P3740 Relation between QT characteristics and transthoracic echocardiographic parameters in patients with uncomplicated isolated mitral valve prolapse

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Background: Sudden death is the least common but obviously the most severe complication of mitral valv prolapse. Some of these patients have been noted to have QT prolongation.Therefore, arrhythmias are likely usual cause of sudden death in patients with MVP. On the other hand complications are more prevalent in those with thickening and redundacy of mitral leaflet and those without leaflet thickening.
The present study was designed to examine between echocardiographic parameters and QT characteristics in with patients uncomplicated and isolated mitral (IMVP) prolapse. Forty-six nonrhaumatic,isolated mitral anterior leaflet prolapse subjects (14 men and 32 women, mean age 25±7) and 24 healthy control subjects (9 men and 15 women, mean age 26±6) were studied. Individuals with accompanying cardiac or systemic disease, or who were on drug therapy that could potentially affect QT characteristics,were excluded. The QT interval was corrected from beggining of d depolarization of the QRS complex to end of the T vawe. Using Bazzet formula, QT interval was corrected (QTC) for heart rate. QTCd was calculated as the difference between the naximum and minimum QT intervals an any of 12 leads. A two dimensional, M mode and Doppler echocardiographic examination was performed. Left atrial diameter and aort diameter were measured with M-mode echocardiography.
Results: There was significant corelation between the amount of billowing leaflet, leaflet thickness, degree of regurgitation and QTC, QCTd in with IMVP. QTC and QTCd correlated positively with the amount of billowing leaflet (respectively: r: 0.33/p<0.04, r: 0.36, p<0.03). QTC and QTCd corelated positively with the leaflet thickness (respectively:r: 0.38/ p<0.02, r:0.4/ p<0.02). In addition, QTC and QTCd corelated positively with degree of regurgitation (respectively:r:0.35/ p<0.03, r:0.4/ p<0.04). But, no corelation were found between any of echocardiographic parameters (LVDD, LVDS, LVEF, FS, AOD, LAD, EDV, ESV) and QT characteristics. Degree of regurgitation was varied mild to moderate.
Conclusions: As a result of the study,it is concluded that the amount of billowing leaflet, leaflet thickness, degree of regurgitation are important parameters in echocardiographic assesment of isolated anterior prolapse.This relation between echocardiographic findings and QTC, QTCd can help to explain unexpected higher sudden death incidence in isolated and uncomplicated mitral valv prolapse subjects.

P3741 Vena contracta width-as a simple method in assessing mitral valve regurgitation. Comparison with Doppler quantitative techniques

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The aim of the present study was to compare vena contracta width with quantitative Doppler methods for assessing mitral regurgitation (MR). Material: 62 patients (pts) with MR (49 men and 13 women), aged from 35 to 84, mean 54 ± 8 years, were covered by the study. The etiology of MR was: coronary artery disease (42 pts), infective endocarditis (4 pts), rheumatic disease (5 pts), dilated cardiomiopathy (5 pts), mitral valve prolapse (6 pts). Exclusion criteria: aortic stenosis and/or aortic insufficiency, mitral stenosis, mechanic prostheses and atrial fibrillation. Patients were included if they had 1 to 4+ MR as defined by Doppler color and angiography. Methods: The mitral regurgitant volume (RV) and effective regurgitant orifice estimated by the proximal convergence method (PISA), regurgitant fraction (RF) calculated using Doppler were compared with vena contracta width (VCW) measured by color Doppler. The angiographic severity of MR was classified as 1 to 4 grades according to the Sellers criteria. Linear regression analysis was used to compare continuous variables. Results were considered statistically significant for p value < 0,05.
Results: The measurements of VCW are expressed as mean value ± SD and presented in table. P value applies to overall comparison of the four grades by ANOVA, comparisons between individual grades were all significant.

Mean values of VCW

Angiographic Grades	VCW (cm)
1	0,31 ± 0,07
2	0,41 ± 0,03
3	0,65 ± 0,23
4	0,85 ± 0,15
p value	<0,001

There was a good correlation between VCW and ERO (r=0,76, p<0,001), RV (r=0,78, p<0,001), RF (r=0,80, p<0,001). VCW also correlated well with angiographic grades of MR (r =0,86, p<0,001).
Conclusions: 1. VCW measured by color Doppler correlates closely with severity of MR. 2. VCW is a simple, reproducible quantitative measurement of MR. 3. VCW can be used in routine practice for noninvasive assessment of MR.

P3742 Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in relation to cardiac contractility

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Background: Functional mitral regurgitation (FMR) in heart failure (HF) results from an inbalance between closing and tethering forces which act on the mitral leaflets. Cardiac resynchronization therapy (CRT) in patients (pts) with intraventricular conduction delay may increase the maximal rate of left ventricular pressure rise (LVdP/dt,mmHg/s), increase the transmitral closing pressure (TMPmax,mmHg) and thereby reduce FMR.
Methods: We tested this hypothesis in 16 pts (mean age 65±7years, QRS>120ms,NYHA III-IV) with at least mild FMR, after implantation of a biventricular (BV) pacemaker system (PM) during no pacing (OFF) and during BV-VDD pacing (mean AV delay 110±19ms). Effective regurgitant orifice area (EROA, mm^2) and regurgitant volume (RV, ml) were measured by the proximal isovelocity surface area Method (PISA). LVdP/dtmax was estimated from CW-Doppler tracings of the FMR jet as the time delay between 1m/s and 3m/s and TMPmax by the maximal velocity of the FMR jet. To quantify temporal changes of TMP, we measured the effective TMP 100ms after onset of FMR (TMP100, mmHg). LV sphericity index (SI) was calculated as the ratio of LV end-diastolic volume and a sphere with a diameter equal to LV end-diastolic long axis.
Results: FMR was acutely reduced with CRT in all pts (table). The relative decrease in EROA (%EROA) correlated linearly to the relative increase in contractility: %EROA=-0.73 x %LVdP/dt-9.9, r=0.81, p<0.01. This was associated with an increase in TMPmax and TMP100. SI at OFF was high with 0.55±0.13 and unaffected by CRT.

	EROA (mm^2)	RV (ml/beat)	TMPmax (mmHg)	TMP100 (mmHg)	LVdP/dtmax (mmHg)
OFF	23±14	32±13	74±26	40±16	554±267
BV-VDD CRT	14±9	21±10	88±27	62±19	740±257
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

Conclusions: CRT acutely reduces FMR severity and this effect is quantitatively related to an increase in LVdP/dtmax. The results support the concept that an accelerated rise in TMP, as demonstrated by the increase in TMP100, may oppose the pathologic mitral leaflet tethering forces and facilitate effective mitral valve closure. This acute effect was independent of changes in LV geometry, which may further contribute to FMR reduction in the long-term.

P3743 Mitral repair combined with CABG improves haemodynamics and clinical status in patients with grade 2 ischaemic mitral regurgitation

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Background: The optimal management of moderate ischemic mild mitral regurgitation (IMR) at the time of CABG is controversial and the decision to repair the valve is often a surgeon's choice.
Objectives: To investigate the influence of surgical repair of grade 2 IMR on clinical outcome of 60 pts who underwent CABG during the last 3 years at our Center
Patients: No difference in age, clinical and hemodynamic conditions, type and number of by pass, cardiopulmonary by-pass strategy were observed preoperatively. All had grade 2 MR at echocardiogram; 30/60 pts (66±7 yr) underwent combined mitral repair (group1) and 30 did not (64±10yrs) (group2). The decision to repair the valve was at surgeon's discretion. Pts were prospectively recalled for a clinical and echocardiographic control. (Mean time from surgery 24 months; min 12, max 36).
Results: Late after surgery pts with mitral repair had significantly lower ventricular volumes, higher EF and lower mean pulmonary artery pressure. In group 1 the degree of MR and NYHA class were significantly lower (p<0.05 and p<0.01 respectively); signs of congestive heart failure (lower limb edema, gallop, cardiomegaly, diastolic dysfunction) were significantly reduced (p<0.03).

Haemodynamic and clinical data

		EDV (mL)	EF (%)	SPP	MR Grade	NYHA
Group 1	Pre-op	163±61	44±11	38±14	2.0±0	2.4±1.04
(repair)	Post-op	137±35b	48±8b	34±11a	0.37±0.6b	0.73±0.7b
Group 2	Pre-op	165±49	39±11	40±13	2.0±0	2.3±0.9
(no repair)	Post-op	168±53c	40±14c	41±12c	1.96±0.7c	1.9±1.1ad

EDV: end-diastolic volume; EF: ejection fraction; SPP: systolic pulmonary pressure (mmHg); MR: mitral regurgitation; a=p<0.05, b=p<0.01 vs pre-op. c=p<0.05, d=p<0.01 between groups.

Conclusions: Mitral repair at the time of CABG in grade 2 IMR improves clinical outcome at intermediate follow-up. Pts have a reduction of symptoms and signs of CHF, a reduction of ventricular volumes and of mean pulmonary pressure as well as an improvement in pump function, in respect to pts who did not have surgical repair.

P3744 Mechanism of exercise-induced dynamic mitral regurgitation in patients with ischaemic left ventricular dysfunction

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To determine the mechanisms of exercise-induced dynamic MR during exercise in patients (pts) with ischemic LV dysfunction, we studied 70 pts with an old infarction and < 50% ejection fraction during semi-supine exercise echocardiography. The infarct location was anterior in 28 pts, inferior in 31 and both anterior and inferior in 11. During test, effective regurgitant orifice (ERO) decreased in 13 pts and increased by < 13 mm^2 in 38 and by > 13 mm^2 in 19. Larger degree of MR at rest was not correlated with larger changes in ERO (r = 0.20). Heart rate, blood pressure and ejection fraction increased similarly in each group. The strongest correlation with ERO changes was observed with the difference in systolic mitral tenting area in all and in inferior infarct pts, whereas coaptation height was the most powerful in anterior infarction pts (r = 0.89, p < 0.0001). In addition, larger changes in mitral systolic area correlated with larger increase in ERO in all infarct categories (r = 0.78, p < 0.0001). For local LV remodeling, posterior displacements of both papillary muscles were associated with larger changes in ERO, whereas lateral displacements showed weaker correlation. Changes in wall motion score index were greater in patients with decreased ERO and inferior location (r = 0.68, p < 0.001). In multivariate analysis, an increase in systolic mitral annular (MA) area independently of the infarct location emerged as an independent predictor of ERO variations. No significant improvement in wall motion score index and an increase in systolic mitral tenting area were also associated with greater changes in ERO in the overall population and in inferior infarct pts. Greater apical mitral leaflet displacement measured as height coaptation distance was selected in anterior infarct pts. We conclude that the degree of dynamic MR are dependent of local LV remodeling (regional wall motion) and mitral valvular deformation (tenting area, systolic MA area) but unrelated to global LV function.

P3745 Does Alfieri's mitral valvuloplasty induce restriction?

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Objective: Alfieri's valvuloplasty could be a limiting factor for exercise tolerance due to the increasing transmitral gradient during stress-test.
Methods: Between June 2000 and June 2001, 15 patients with an echographic grade 3 to 4 mitral regurgitation were operated on according to Alfieri's technique. The mean age was 64.3 ± 16.2 years. In 9 cases, there was a bileaflet prolapsed degenerative valve, in 5 cases there was a pure or associated ischemic mitral regurgitation, and in 1 case an endocarditis on Barlow disease. The operation consisted on suturing the free margins of the prolapsed segments of the two leaflets in 100% of cases. Associated procedures were Carpentier's ring annuloplasty in 66.6% and CABG in 13% of cases. After a mean of follow-up of 5 months, all patient were seen at the outpatient clinic for a clinical evaluation, an echocardiogram, and a cardiorespiratory exercise testing with maximal oxygen uptake (VO2 max) recording.
Results: There was no early or late death. Improvement of the NYHA class was observed in all patients with a conversion from a mean preoperative value of 2.9 ± 1.2 to a postoperative value of 1.3 ± 0.5 (p= 0.0002). Only 13% of patients have had a residual mitral regurgitation. In all cases there was a lowering of the arterial systolic pulmonary pressure from a mean of 48 ± 18 mmHg preoperatively to 36 ± 11 mmHg postoperatively (p= 0.03) and LVEF remained unchanged from 57± 10 to 62± 14% (p=0.26). The mean transmitral gradient was 4.2 ± 1.2 at rest and increased to 8.2 ± 3.4mmHg during peak exercise(p= 0.005) The mean mitral area was 2.3 ± 0.6cm^2. Among the 12 interpretable cardiorespiratory exercise testing, 7 patients have normal exercise tolerance (86.6% mean VO2 max for a >85% normal value), 4 patients have a cardiogenic limitation (62.5% mean VO2 max), and one young patient have a muscular exercise limitation (68% VO2 max) due to exercise deconditioning.
Conclusion: Alfieri's valvuloplasty is a simple and reliable technique in case of bileaflet prolapsed mitral valve on aged patients. According to these results, even if there appear a restrictive aspect of the repair like demonstrated by the valve area and the transvalvular gradient, his impact on clinical status seems moderate.

P3746 Effect of prosthetic ring annuloplasty on mitral leaflet motion: an echocardiography study

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Objective: Prosthetic ring annuloplasty for mitral valve repair may indirectly influence leaflet motion. The aim of this study was to assess i)the geometric changes of the left ventricle base following ring insertion and ii) their impact of leaflet mobility.
Methods: Twenty-five patients with mitral valve regurgitation who underwent a valve repair were studied with intraoperative multiplane transesophageal echocardiography (TEE) before and after prosthetic ring annuloplasty. Patients who required a repair involving the anterior leaflet were excluded. Three parameters were measured: the antero posterior mitral valve annulus diameter (MAD), the angle between aortic and mitral annuli planes (AMA), the angle between anterior leaflet and mitral annulus plane (ALA). Acquisition of the 3 parameters was performed at end-systolic and maximal diastolic valve opening; using midoesophageal 3-chambers and longitudinal echocardiographic view. Anterior leaflet excursion throughout the cardiac cycle was calculated according to: ALE = diastolic ALA - systolic ALA.
Results: Mitral valve repair techniques were: posterior leaflet resection with annuloplasty (n=19) or annuloplasty alone: flexible Duran ring (n=6). All patients had a excellent functional result with no (n=18) or mild (n=7) mitral regurgitation. There was no significant difference between systolic and diastolic MAD. The MAD was significantly reduced after repair from 37±5mm to 20±3mm ($p<0.001$). The AMA decreased from 115±10 degrees to 105±9 degree ($p<0.001$). The ALA, in systole, increased from 19±5 degrees to 26±6 degrees ($p=0.001$). The ALA in diastole remained unchanged (midesophageal 3-chambers and longitudinal views). Anterior leaflet excursion decreased from 32±11 degrees to 24±10 at midesophageal 3 chambers view and from 42±13 degrees to 33±11 degrees at longitudinal view after repair($p=0.001$).
Conclusion: Leaflet mobility is slightly reduced following ring annuloplasty. Leaflet restriction occurs simultaneously to geometric changes of the left ventricular base as illustrated by a decrease in mitral annulus diameter and a reduction of the aorto-mitral angle. This probably account for an increased chordal tension resulting in usual findings following annuloplasty such as: "spontaneus" correction of a slight anterior leaflet prolapse, motionless aspect of the posterior leaflet.

P3747 Left atrial function and apoptotic markers in mitral regurgitation: effect of valvular replacement

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Purpose: Patients with mitral regurgitation (MR) and heart failure (HF) are characterized by left atrial (LA) function changes and apoptotic process activation. This study was undertaken with the purpose of evaluating the effect of valve replacement on the LA function and apoptotic markers of patiens with MR and HF, and to examine their relationship.
Methods: We studied 35 patients in sinus rhythm (mean age 56.2±4.6 years, range 30 to 69), with MR and HF (12 in NYHA II, 13 in NYHA III, and 10 in NYHA III-IV) and 20 age- and gender-matched normal volunteers (G3). Peripheral blood was sampled before (2±4 days, G1) and 6 months postoperatively (G2) and was evaluated for plasma levels of soluble Fas/APO-1 receptor (sFas, ng/ml), TNF-alpha (pg/ml) and Interleukin-6 (IL-6, pg/ml) measured by ELISA method. LA volumes (cm^3) were measured echocardiographically before (G1) and 6 months postoperatively (G2) at mitral valve opening (maximal, Vmax), at onset of left atrial systole (P wave of the electrocardiogram, Vp) and at mitral valve closure (minimal, Vmin) from the apical (2) and (4) chamber views using the biplane are-length method. LA contractile function was assessed with the LA active emptying fraction (ACTEF) = (Vp-Vmin)/Vp.
Results are shown in the table.

	sFas	TNF-a	IL-6	Vmax	ACTEF
G1	8.6±1.8	7.6±1.6	7,2±1.1	124±20	0.25±0.08
G2	6.4±1.7b	5.3±1.9b	5.4±1.0b	88±16a	0.28±0.07b
G3	2.1±0.4a	4.1±0.8a	3.8±0.9a	46±10a	0.35±0.10a

a:$p<0.001$ vs. G1, b:$p<0.01$ vs.G1

A significant negative relation was noticed between ACTEF and sFas, TNF-a and IL-6 levels ($r=-0.76$, $p<0.001$, $r=-0.80$, $p<0.01$ and $r=-0.76$, $p<0.01$, respectively).
Conclusions: Valvular replacement for mitral regurgitation reduces LA atrial size and improves LA contractile function. The latter is probably due to the postoperative inversion of the apoptotic process.

P3748 The calcified mitral ring: a potential site for a severe type of bacterial endocarditis

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Bacterial endocarditis usually occurs on valve leaflets previously damaged by other disease processes. Ageing induces degenerative, calcific lesions that become increasing causes of endocarditis, but mitral annular calcification (MAC) is still not considered to date as a predisposing factor.
Methods: We conducted a prospective study among patients referred for suspected infective endocarditis (IE). Fourty consecutive patients with proven infective IE of the native mitral valve were included. All the patients underwent multiplane transesophageal echocardiography (TEE), with special attention paid to the presence of MAC, and to the attachment site of the vegetations. Patients with vegetations on the valve leaflets were compared to those where vegetations were seen attached to the mitral annulus.
Results: Among the 40 patients, 30 were found to have classical mitral leaflet endocarditis (group 1), whereas the other 10 (25%) had vegetations specifically involving the mitral ring (group 2). Thirteen % of group 1 patients had mild MAC, but all group 2 patients had moderate to severe MAC. Group 2 patients were older (71 vs 66, NS), had more frequently hypertension (60% vs 30%, NS), chronic renal failure (20% vs 6.7%, NS), cirrhosis (30% vs 6.7%, $p=0.09$), diabetes mellitus (80% vs 16.7%, $p<0.005$) and cancers (50% vs 13.3%, $p<0.05$) than group 1 patients. Staphylococcus was the causative organism in 70% of group 2 patients, whereas Streptococcus was predominant in group 1. Echocardiographic findings in group 2 patients compared to other patients were significantly different regarding vegetation size (25.6 ± 16.5 vs 11.9 ± 8 mm), and occurrence of (1) calcifications within the vegetation (80% ± 7.5%), (2) mitral ring abscess (60% vs 0), and (3) para-annular perforation of the posterior mitral leaflet (70% vs 0). Finally, clinical outcome in group 2 patients was very pejorative, with clinical features of meningoencephalitis in 60%, stroke in 30%, and an in-hospital mortality rate of 70% compared to 30% in the other group.
Conclusion: bacterial endocarditis involving MAC in an unrecognized type of IE characterized by high prevalence of Staphylococcus, particular echocardiographic appearance of large, calcified vegetations attached to the posterior part of the mitral annulus, high frequency of annular abscesses, and poor outcome due to the occurrence in elderly patients with serious co-existing diseases, including diabetes, chronic renal failure, cirrhosis and cancers.